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(54) Title: PHENOXYBENZYLAMINE DERIVATIVES AS SELECTIVE SEROTONIN RE-UP TAKE INHIBITORS

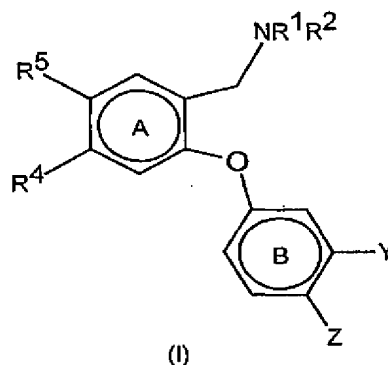
(57) Abstract: A compound of general formula (I) wherein R¹ and R² are H, C₁-C₆alkyl or (CH₂)_d(C₃-C₆cycloalkyl) wherein d = 0, 1, 2 or 3; or R¹ and R² together with the nitrogen to which they are attached from an azetidine ring; Z or Y is -SR³ and the other Z or Y is halogen or -R³; wherein R³ is C₁-C₄ alkyl optionally substituted with fluorine; except that R³ is not CF₃; or Z and Y are linked so that, together with the interconnecting atoms, Z and Y form a fused 5 to 7-membered carbocyclic or heterocyclic ring, and wherein when Z and Y form a heterocyclic ring, in addition to carbon atoms, the linkage contains one or two heteroatoms independently selected from oxygen, sulfur and nitrogen; R⁴ and R⁵, which may be the same or different, are: A-X, wherein A = -CH=CH- or -(CH₂)_p- where p is 0, 1 or 2; X is hydrogen, F, Cl, Br, I, CONR⁶R⁷, SO₂NR⁶R⁷, SO₂NHC(=O)R⁶, OH, C₁₋₄alkoxy, NR⁸SO₂R⁹, NO₂, NR⁶R¹¹, CN, CO₂R¹⁰, CHO, SR¹⁰, S(O)R⁹ or SO₂R¹⁰; or a 5- or 6-membered heterocyclic ring containing 1, 2 or 3 heteroatoms selected from N, S and O, optionally substituted independently by one or more R¹³; wherein R¹³ is hydroxy, C₁-C₄alkoxy, F, C₁-C₆alkyl, haloalkyl, haloalkoxy, -NH₂, NH(C₁-C₆alkyl) or -N(C₁-C₆alkyl)₂. The compounds of general formula (I) inhibit monoamine reuptake and in particular exhibit activity as selective serotonin reuptake inhibitors.

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PHENOXYBENZYLAMINE DERIVATIVES AS SELECTIVE SEROTONIN RE-UPTAKE INHIBITORS

This invention relates to novel diphenyl ether compounds which inhibit monoamine re-uptake. In particular compounds of the present invention exhibit activity as selective
 5 serotonin re-uptake inhibitors (SSRIs) and have utility therefore in a variety of therapeutic areas. Notably the compounds of the present invention are useful in the treatment or prevention of a variety of disorders, including those in which the regulation of monoamine transporter function is implicated, such as depression, attention deficit
 10 hyperactivity disorder, obsessive-compulsive disorder, post-traumatic stress disorder, substance abuse disorders and sexual dysfunction including premature ejaculation, and to pharmaceutical formulations containing such compounds.

According to a first aspect, the invention provides a compound of general formula (I), pharmaceutically acceptable salts, solvates or polymorphs thereof;



15

wherein;

R^1 and R^2 , which may be the same or different, are H, C_1 - C_6 alkyl or

$(CH_2)_d(C_3-C_6$ cycloalkyl) wherein $d = 0, 1, 2$ or 3 ; or R^1 and R^2 together with the nitrogen to which they are attached form an azetidine ring;

20 Z or Y is $-SR^3$ and the other Z or Y is halogen or $-R^3$; wherein R^3 is independently C_1 - C_4 alkyl optionally substituted with fluorine; except that R^3 is not CF_3 ;

or Z and Y are linked so that, together with the interconnecting atoms, Z and Y form a fused 5 to 7-membered carbocyclic or heterocyclic ring which may be saturated, unsaturated or aromatic, and wherein when Z and Y form a heterocyclic ring, in
 25 addition to carbon atoms, the linkage contains one or two heteroatoms

independently selected from oxygen, sulfur and nitrogen; with the proviso that when R^5 is fluorine and R^2 is methyl then the fused ring is not 1,3-dioxolane and Z and Y together do not form a fused phenyl ring;

R⁴ and R⁵, which may be the same or different, are:

A-X, wherein A = -CH=CH- or -(CH₂)_p- where p is 0, 1 or 2; X is hydrogen, F, Cl, Br, I, CONR⁶R⁷, SO₂NR⁶R⁷, SO₂NHC(=O)R⁶, OH, C₁₋₄alkoxy, NR⁸SO₂R⁹, NO₂, NR⁶R¹¹, CN, CO₂R¹⁰, CHO, SR¹⁰, S(O)R⁹ or SO₂R¹⁰; R⁶, R⁷, R⁸ and R¹⁰ which may be the same or different, are hydrogen or C₁₋₆alkyl optionally substituted independently by one or more R¹²; R⁹ is C₁₋₆alkyl optionally substituted independently by one or more R¹²; R¹¹ is hydrogen, C₁₋₆alkyl optionally substituted independently by one or more R¹², C(O)R⁶, CO₂R⁹, C(O)NHR⁶ or SO₂NR⁶R⁷; R¹² is F (preferably up to 3), OH, CO₂H, C₃₋₆cycloalkyl, NH₂, CONH₂, C₁₋₆alkoxy, C₁₋₆alkoxycarbonyl or a 5- or 6-membered heterocyclic ring containing 1, 2 or 3 heteroatoms selected from N, S and O optionally substituted independently by one or more R¹³; or R⁶ and R⁷, together with the nitrogen to which they are attached, form a 4-, 5- or 6-membered heterocyclic ring optionally substituted independently by one or more R¹³; or
a 5- or 6-membered heterocyclic ring containing 1, 2 or 3 heteroatoms selected from N, S and O, optionally substituted independently by one or more R¹³; wherein R¹³ is hydroxy, C₁₋₄alkoxy, F, C₁₋₆alkyl, haloalkyl, haloalkoxy, -NH₂, -NH(C₁₋₆alkyl) or -N(C₁₋₆alkyl)₂.

Unless otherwise indicated, any alkyl group may be straight or branched and is of 1 to 6 carbon atoms, preferably 1 to 4 and particularly 1 to 3 carbon atoms.

Unless otherwise indicated, any carbocyclyl group contains 3 to 8 ring-atoms, and may be saturated, unsaturated or aromatic. Preferred saturated carbocyclyl groups are cyclopropyl, cyclopentyl or cyclohexyl. Preferred unsaturated carbocyclyl groups contain up to 3 double bonds. A preferred aromatic carbocyclyl group is phenyl. The term carbocyclic should be similarly construed. In addition, the term carbocyclyl includes any fused combination of carbocyclyl groups, for example naphthyl, phenanthryl, indanyl and indenyl.

Unless otherwise indicated, any heterocyclyl group contains 5 to 7 ring-atoms up to 4 of which may be hetero-atoms such as nitrogen, oxygen and sulfur, and may be saturated, unsaturated or aromatic. Examples of heterocyclyl groups are furyl, thienyl, pyrrolyl, pyrrolinyl, pyrrolidinyl, imidazolyl, dioxolanyl, oxazolyl, thiazolyl, imidazolyl, imidazoliny,

imidazolidinyl, pyrazolyl, pyrazolinyl, pyrazolidinyl, isoxazolyl, isothiazolyl, oxadiazolyl, triazolyl, thiadiazolyl, pyranyl, pyridyl, piperidinyl, dioxanyl, morpholino, dithianyl, thiomorpholino, pyridazinyl, pyrimidinyl, pyrazinyl, piperazinyl, sulfolanyl, tetrazolyl, triazinyl, azepinyl, oxazepinyl, thiazepinyl, diazepinyl and thiazolinyl. In addition, the term
5 heterocyclyl includes fused heterocyclyl groups, for example benzimidazolyl, benzoxazolyl, imidazopyridinyl, benzoxazinyl, benzothiazinyl, oxazolopyridinyl, benzofuranyl, quinoxalinyl, quinazolinyl, quinoxalinyl, dihydroquinazolinyl, benzothiazolyl, phthalimido, benzofuranyl, benzodiazepinyl, indolyl and isoindolyl. The term heterocyclic should be similarly construed.

10

Halo means fluoro, chloro, bromo or iodo.

Preferably R^1 and R^2 , which may be the same or different, are hydrogen or C_1 - C_6 alkyl. More preferably hydrogen or methyl.

15

When Z or Y is $-SR^3$, R^3 is preferably methyl or ethyl.

When Z and Y form a fused ring, the ring is preferably a heterocyclic ring. More preferably, the linkage contains one or two sulfur atoms.

20

Preferably R^4 and R^5 are not both hydrogen.

Preferably R^4 and R^5 , which may be the same or different, are

25 $-(CH_2)_p-X$, where p is 0, 1 or 2 (preferably 0 or 1); X is hydrogen, hydroxy, $CONR^6R^7$, $SO_2NR^6R^7$, $NR^8SO_2R^9$, SR^{10} , SOR^9 or SO_2R^{10} wherein R^6 , R^7 , R^8 , R^9 and R^{10} are as defined in the first aspect, or

a 5- or 6-membered heterocyclic ring containing 1, 2 or 3 heteroatoms selected from N, S and O (preferably oxadiazolyl, triazolyl, imidazolyl, oxazolyl, pyrazolyl, pyridinyl or pyrimidinyl).

30

More preferably R^4 and R^5 , which may be the same or different, are:

$-(CH_2)_p-X$, where p is 0 or 1; X is hydrogen, hydroxy, $CONR^6R^7$, $SO_2NR^6R^7$ or $NR^8SO_2R^9$; wherein R^6 and R^7 , which may be the same or different, are hydrogen or C_1 - C_3 alkyl optionally substituted by hydroxy, $-CONH_2$ or C_1 - C_3 alkoxy (preferably

methoxy); R^8 is hydrogen, hydroxyethyl or methyl; or R^9 is methyl, ethyl, isopropyl, trifluoromethyl or methoxyethyl; or triazolyl, imidazolyl or pyrazolyl.

- 5 More preferably still R^4 is hydrogen.

- Preferably R^6 and R^7 , which may be the same or different, are hydrogen, C_1 - C_3 alkyl optionally substituted by hydroxy, $-CONH_2$ or C_1 - C_3 alkoxy (preferably methoxy). More preferably R^6 and R^7 , which may be the same or different, are hydrogen or methyl, more preferably still hydrogen.
- 10

When present, R^{12} is preferably oxadiazolyl, triazolyl, imidazolyl, oxazolyl, pyrazolyl, pyridinyl or pyrimidinyl. More preferably triazolyl, imidazolyl or pyrazolyl.

- 15 In the case where R^6 and R^7 , together with the nitrogen to which they are attached, form a heterocyclic ring, preferred rings are pyrrolidine or piperidine rings each of which may be substituted by OH or $CONH_2$ or a morpholine ring which may be substituted by $CONH_2$.
- 20 Preferably R^{11} is hydrogen or C_{1-6} alkyl.

Preferably R^8 is hydrogen, hydroxyethyl or methyl. More preferably hydrogen.

- Preferably R^9 is methyl, ethyl, isopropyl, trifluoromethyl or methoxyethyl. More preferably methyl or ethyl (preferably methyl).
- 25

Preferably R^{10} is methyl or ethyl.

Preferably p is 1 or 0, more preferably 0.

30

Preferably

R^1 and R^2 , which may be the same or different, are hydrogen or methyl;

when present, R^3 is methyl or ethyl; or Z and Y are linked so that, together with the interconnecting atoms, Z and Y form a fused 5 to 7-membered carbocyclic or

- 35 heterocyclic ring which may be saturated, unsaturated or aromatic, and wherein

when Z and Y form a heterocyclic ring, in addition to carbon atoms, the linkage contains one or two heteroatoms independently selected from oxygen, sulfur and nitrogen; and

R⁴ and R⁵, which may be the same or different, are

- 5 (CH₂)_p-X, where p is 0 or 1; X is hydrogen, hydroxy, CONR⁶R⁷, SO₂NR⁶R⁷, NR⁸SO₂R⁹, SR¹⁰, SOR⁹ or SO₂R¹⁰ and wherein R⁶ and R⁷, which may be the same or different, are hydrogen, C₁-C₃alkyl optionally substituted by hydroxy, -CONH₂ or C₁-C₃alkoxy (preferably methoxy); or R⁶ and R⁷, together with the nitrogen to which they are attached, may form a morpholine, pyrrolidine or piperidine ring
- 10 each of which may be substituted by OH or CONH₂; R⁸ is hydrogen, hydroxyethyl or methyl (preferably hydrogen); R⁹ is methyl, ethyl, isopropyl, trifluoromethyl or methoxyethyl; and R¹⁰ is methyl or ethyl; or
- an oxadiazolyl, triazolyl, imidazolyl, oxazolyl, pyrazolyl, pyridinyl or pyrimidinyl group.

- 15 More preferably

R¹ and R², which may be the same or different, are hydrogen or methyl;

when present, R³ is methyl or ethyl; or Z and Y are linked so that, together with the interconnecting atoms, Z and Y form a fused 5 to 7-membered heterocyclic ring containing 1 or 2 sulfur atoms; and

- 20 R⁴ and R⁵, which may be the same or different, are
- (CH₂)_p-X, where p is 0 or 1; X is hydrogen, hydroxy, CONR⁶R⁷, SO₂NR⁶R⁷ or NR⁸SO₂R⁹; wherein R⁶ and R⁷, which may be the same or different, are hydrogen, C₁-C₃alkyl optionally substituted by hydroxy, -CONH₂ or C₁-C₃alkoxy (preferably methoxy); R⁸ is hydrogen, hydroxyethyl or methyl; R⁹ is methyl, ethyl, isopropyl,
- 25 trifluoromethyl or methoxyethyl; or
- triazolyl, imidazolyl or pyrazolyl.

More preferably still

R¹ and R², which may be the same or different, are hydrogen or methyl;

- 30 when present R³ is methyl or ethyl; or Z and Y are linked so that, together with the interconnecting atoms, Z and Y form a fused saturated 5 to 7-membered heterocyclic ring containing 1 or 2 sulfur atoms;

R⁴ is hydrogen, and

R⁵ is

$-(CH_2)_p-X$, where p is 0 or 1; X is hydrogen, hydroxy, $CONR^6R^7$, $SO_2NR^6R^7$ or $NR^6SO_2R^9$;
 wherein R^6 and R^7 , which may be the same or different, are hydrogen, C_1-C_3 alkyl
 optionally substituted by hydroxy, $-CONH_2$ or C_1-C_3 alkoxy (preferably methoxy);
 R^8 is hydrogen, hydroxyethyl or methyl; R^9 is methyl, ethyl, isopropyl,
 5 trifluoromethyl or methoxyethyl; or
 triazolyl, imidazolyl or pyrazolyl.

More preferably still R^4 and R^5 are not both hydrogen.

10 Preferred compounds are:

4-(2,3-dihydro-1-benzothien-5-yloxy)-3-[(methylamino)methyl]-benzenesulfonamide
 (Example 2);

3-[(dimethylamino)methyl]-4-[3-methyl-4-(methylsulfanyl)phenoxy]-benzenesulfonamide
 (Example 12);

15 4-(2,3-dihydro-1-benzothien-5-yloxy)-3-[(dimethylamino)methyl]-benzenesulfonamide
 (Example 16);

4-[3-chloro-4-(methylsulfanyl)phenoxy]-3-[(dimethylamino)methyl]-benzenesulfonamide
 (Example 17);

3-[(dimethylamino)methyl]-4-[3-fluoro-4-(methylsulfanyl)phenoxy]-benzenesulfonamide
 20 (Example 18);

N,N-dimethyl-*N*-[2-(6-quinolinylloxy)benzyl]amine (Example 29);

3-[(methylamino)methyl]-4-(6-quinolinylloxy)benzenesulfonamide (Example 35);

4-(2,3-dihydro-1-benzothien-5-yloxy)-3-[(methylamino)methyl]benzamide (Example 60);

4-(2,3-dihydro-1-benzothien-5-yloxy)-*N*-methyl-3-[(methylamino)methyl]-benzamide
 25 (Example 62);

N-{3-[(methylamino)methyl]-4-[3-methyl-4-(methylsulfanyl)phenoxy]benzyl}methanesulfonamide (Example 75);

3-[(methylamino)methyl]-4-[3-methyl-4-(methylsulfanyl)phenoxy]benzamide (Example
 79);

30 4-(2,3-dihydro-1,4-benzoxathiin-7-yloxy)-3-[(dimethylamino)methyl]benzamide (Example
 88);

{3-[(dimethylamino)methyl]-4-[3-fluoro-4-(methylsulfanyl)phenoxy]phenyl}-methanol
 (Example 90);

3-[(dimethylamino)methyl]-4-(6-quinolinylloxy)benzamide (Example 100);

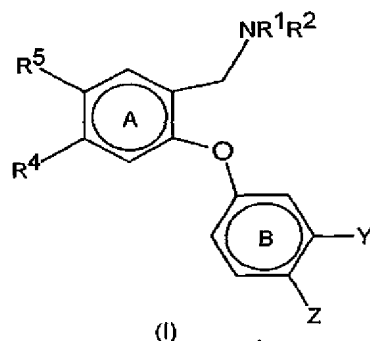
35 3-[(methylamino)methyl]-4-(6-quinolinylloxy)benzamide (Example 102);

N-methyl-*N*-{3-[(methylamino)methyl]-4-[3-methyl-4-(methylsulfonyl)phenoxy]-phenyl}methanesulfonamide (Example 116) and

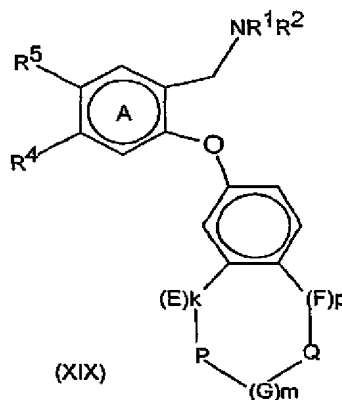
N-{4-(2,3-dihydro-1,4-benzoxathiin-7-yloxy)-3-[(dimethylamino)methyl]phenyl}-methanesulfonamide (Example 124).

5

According to a second aspect the invention provides compound of formula (I) or (XIX)



- and pharmaceutically acceptable salts or solvates thereof wherein (in this aspect): R^1 and R^2 independently represent H, C_1 - C_6 alkyl or $(CH_2)_d(C_3$ - C_8 cycloalkyl) wherein $d = 0$, 1, 2 or 3, or wherein NR^1R^2 when taken together represent a 4-membered ring wherein R^1 and R^2 together represent C_3 alkyl; Z and Y both independently represent $-SR^3$ wherein, when $Z = -SR^3$ then $Y = \text{halogen}, -OR^a, -R^a$ or $-SR^a$; or when $Y = -SR^3$ then $Z = \text{halogen}, -OR^a, R^a$ or $-SR^a$; and R^3 and R^a independently represent: C_1 - C_4 alkyl (optionally substituted with fluorine atoms e.g. $-CF_3$); or Z and Y when taken together can represent a fused 5 to 7 membered ring as illustrated by general formula XIX, wherein said 5 to 7 membered ring may be saturated, unsaturated or aromatic, and wherein said 5 to 7 membered ring may optionally contain one or more heteroatoms P and Q, wherein P and Q may be independently O, S or N, and wherein E, F, or G independently represent CH or CH_2 and wherein k and p may independently be = 0, 1, 2 or 3, and m = 1, 2 or 3; and



R^4 and R^5 independently represent $A-X$ wherein $A = -(CH_2)_n-$, wherein n represents 0, 1 or 2 and wherein X represents: H, F, Cl, Br, I, $CONR^6R^7$ or $SO_2NR^6R^7$, OH, $NR^8SO_2R^9$, NO_2 , NR^6R^{11} , CN, CO_2R^{10} , CHO, $S(O)_mR^{10}$ wherein $m = 0, 1$ or 2 and wherein R^6, R^7, R^8 and R^{10} independently represent H or C_{1-6} alkyl, wherein R^9 represents C_{1-6} alkyl, R^{11} represents H, C_{1-6} alkyl, $C(O)R^6$, CO_2R^9 , $C(O)NHR^6$ or $SO_2NR^6R^6$ and wherein said C_{1-6} alkyl group is optionally substituted by one or more groups selected from OH, CO_2H , C_{3-6} cycloalkyl, NH_2 , $CONH_2$, C_{1-6} alkoxy, C_{1-6} alkoxy carbonyl and a 5- or 6-membered heterocyclic ring containing 1, 2 or 3 heteroatoms selected from N, S and O; or with the proviso that when $P=Q=$ oxygen then both k and p are not zero; with the proviso that Z and Y together do not form a fused phenyl ring; R^4 or R^5 may be representative of a 5- or 6-membered heterocyclic ring containing 1, 2 or 3 heteroatoms selected from N, S and O; and in addition, R^6 and R^7 may, together with the N atom to which they are attached, represent a 5- or 6- membered heterocyclic ring which may be optionally substituted; and pharmaceutically acceptable salts or solvates thereof with the proviso that both R^4 and R^5 are not H.

For the avoidance of doubt, unless otherwise indicated, the term substituted means substituted by one or more defined groups. In the case where groups may be selected from a number of alternatives groups, the selected groups may be the same or different.

For the avoidance of doubt, the term independently means that where more than one substituent is selected from a number of possible substituents, those substituents may be the same or different.

According to a third aspect, the invention provides a compound of general formula I and pharmaceutically acceptable salts thereof, wherein R^1, R^2, R^3, Z and Y are as defined in the first aspect; and R^4 and R^5 , which may be the same or different, are $-(CH_2)_p-A'$, wherein p is 0, 1 or 2 and A' is a polar group. In this aspect, polar groups may be defined as those having a negative π -value (see C Hansch and A Leo, 'Substituent Constants for Correlation Analysis in Chemistry and Biology', Wiley, New York, 1979). In this system, H has a π -value of 0.00, $-OCH_3$ has a π -value of -0.02 , and $-SO_2NH_2$ has a π -value of -1.82 , for example [see Table VI-I, 'Well-Characterized Aromatic Substituents', p 49, *ibid*]. More preferred polar groups have a more negative π -value: thus, preferred groups have π -values of a greater negative value than -0.1 , more preferably a greater negative value than -0.5 , and most preferably a greater negative value than -1.0 . Even when p is other

than zero in the above definition, the definition of A' is based on the above reference as if p was zero.

Unless otherwise specified, the compounds of the first, second and third aspects are
5 hereinafter defined as compounds of the invention.

The compounds of the invention have the advantage that they are selective inhibitors of the re-uptake of serotonin (SRIs) (and so are likely to have reduced side effects), they have a rapid onset of action (making them suitable for administration shortly before an
10 effect is required), they have desirable potency and associated properties. Compounds that selectively inhibit the re-uptake of serotonin, but not noradrenaline or dopamine, are preferred.

We have found that compounds of formula I which possess these properties have a
15 relatively polar group at R⁴/R⁵.

The pharmaceutically or veterinarily acceptable salts of the compounds of formula I which contain a basic centre are, for example, non-toxic acid addition salts formed with inorganic acids such as hydrochloric, hydrobromic, hydroiodic, sulfuric and phosphoric
20 acid, with carboxylic acids or with organo-sulfonic acids. Examples include the HCl, HBr, HI, sulfate or bisulfate, nitrate, phosphate or hydrogen phosphate, acetate, benzoate, succinate, saccharate, fumarate, maleate, lactate, citrate, tartrate, gluconate, camsylate, methanesulfonate, ethanesulfonate, benzenesulfonate, p-toluenesulfonate and pamoate salts. Compounds of the invention can also provide pharmaceutically or veterinarily
25 acceptable metal salts, in particular non-toxic alkali and alkaline earth metal salts, with bases. Examples include the sodium, potassium, aluminium, calcium, magnesium, zinc, diolamine, olamine, ethylenediamine, tromethamine, chloine, megulamine and diethanolamine salts. For reviews on suitable pharmaceutical salts see Berge *et al*, J. Pharm, Sci., 66, 1-19, 1977; P L Gould, International Journal of Pharmaceutics, 33
30 (1986), 201-217; and Bighley *et al*, Encyclopedia of Pharmaceutical Technology, Marcel Dekker Inc, New York 1996, Volume 13, page 453-497.

Hereinafter, the compounds, their pharmaceutically acceptable salts, their solvates and polymorphs, defined in any aspect of the invention (except intermediate compounds in
35 chemical processes) are referred to as "compounds of the invention".

The pharmaceutically acceptable solvates of the compounds of the invention include the hydrates thereof.

- 5 The compounds of the invention may possess one or more chiral centres and so exist in a number of stereoisomeric forms. All stereoisomers and mixtures thereof are included in the scope of the present invention. Racemic compounds may either be separated using preparative HPLC and a column with a chiral stationary phase or resolved to yield individual enantiomers utilising methods known to those skilled in the art. In addition,
10 chiral intermediate compounds may be resolved and used to prepare chiral compounds of the invention.

In cases where the compounds of the invention exist as the E and Z isomers, the invention includes individual isomers as well as mixtures thereof.

15

In cases where compounds of the invention exist as tautomeric isomers, the invention includes individual tautomers as well as mixtures thereof.

- In cases where the compounds of the invention exist as optical isomers, the invention
20 includes individual isomers as well as mixtures thereof.

In cases where the compounds of the invention exist as diastereoisomers, the invention includes individual diastereoisomers as well as mixtures thereof.

- 25 Separation of diastereoisomers or E and Z isomers may be achieved by conventional techniques, e.g. by fractional crystallisation, chromatography or H.P.L.C. An individual enantiomer of a compound of the invention may be prepared from a corresponding optically pure intermediate or by resolution, such as by H.P.L.C. of the corresponding racemate using a suitable chiral support or by fractional crystallisation of the
30 diastereoisomeric salts formed by reaction of the corresponding racemate with a suitable optically active acid or base, as appropriate.

- The compounds of the invention may exist in one or more tautomeric forms. All tautomers and mixtures thereof are included in the scope of the present invention. For
35 example, a claim to 2-hydroxypyridinyl would also cover its tautomeric form, α -pyridonyl.

It will be appreciated by those skilled in the art that certain protected derivatives of compounds of the invention, which may be made prior to a final deprotection stage, may not possess pharmacological activity as such, but may, in certain instances, be
5 administered orally or parenterally and thereafter metabolised in the body to form compounds of the invention which are pharmacologically active. Such derivatives may therefore be described as "prodrugs". Further, certain compounds of the invention may act as prodrugs of other compounds of the invention.

10 All protected derivatives and prodrugs of compounds of the invention are included within the scope of the invention. Examples of suitable pro-drugs for the compounds of the present invention are described in *Drugs of Today*, Volume 19, Number 9, 1983, pp 499 – 538 and in *Topics in Chemistry*, Chapter 31, pp 306 – 316 and in "Design of Prodrugs" by H. Bundgaard, Elsevier, 1985, Chapter 1 (the disclosures in which documents are
15 incorporated herein by reference).

It will further be appreciated by those skilled in the art, that certain moieties, known to those skilled in the art as "pro-moieties", for example as described by H. Bundgaard in "Design of Prodrugs" (the disclosure in which document is incorporated herein by
20 reference) may be placed on appropriate functionalities when such functionalities are present within the compounds of the invention.

Preferred prodrugs for compounds of the invention include: esters, carbonate esters, hemi-esters, phosphate esters, nitro esters, sulfate esters, sulfoxides, amides, carbamates, azo-
25 compounds, phosphamides, glycosides, ethers, acetals and ketals.

The invention also includes all suitable isotopic variations of the compounds of the invention. An isotopic variation is defined as one in which at least one atom is replaced by an atom having the same atomic number but an atomic mass different from the
30 atomic mass usually found in nature. Examples of isotopes that can be incorporated into compounds of the invention include isotopes of hydrogen, carbon, nitrogen, oxygen, phosphorus, sulphur, fluorine and chlorine such as ^2H , ^3H , ^{13}C , ^{14}C , ^{15}N , ^{17}O , ^{18}O , ^{31}P , ^{32}P , ^{35}S , ^{18}F and ^{36}Cl , respectively. Certain isotopic variations of the invention, for example, those in which a radioactive isotope such as ^3H or ^{14}C is incorporated, are useful in drug
35 and/or substrate tissue distribution studies. Tritiated, i.e. ^3H , and carbon-14, i.e. ^{14}C

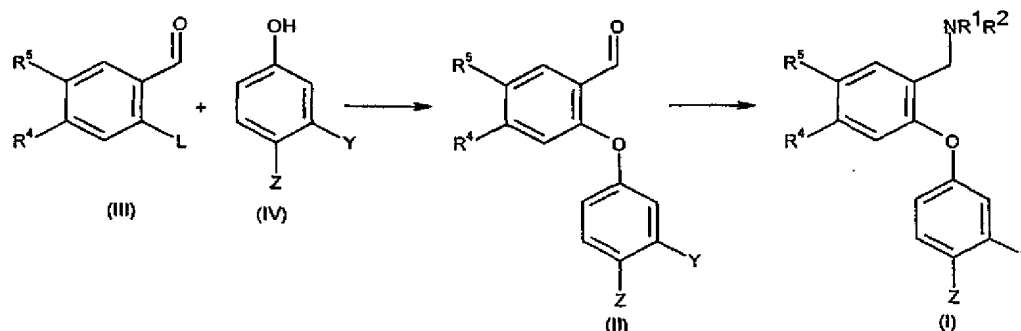
isotopes are particularly preferred for their ease of preparation and detectability. Further, substitution with isotopes such as deuterium, i.e. ^2H , may afford certain therapeutic advantages resulting from greater metabolic stability, for example, increased *in vivo* half-life or reduced dosage requirements and hence may be preferred in some circumstances. Isotopic variations of the compounds of the invention can generally be prepared by conventional procedures such as by the methods or preparations described in the Examples and Preparations hereafter using appropriate isotopic variations of suitable reagents.

- 10 Compounds of the invention may be prepared, in known manner in a variety of ways. In the following reaction schemes and hereafter, unless otherwise stated, R^1 to R^{13} , Z and Y are as defined in the first aspect. These processes form further aspects of the invention.

- 15 Throughout the specification, general formulae are designated by Roman numerals I, II, III, IV etc. Subsets of these general formulae are defined as Ia, Ib, Ic etc, IVa, IVb, IVc etc.

- Compounds of general formula (I) may be prepared from compounds of formula (II) by reaction with an amine of general formula HNR^1R^2 , or with a suitable salt form thereof, together with a hydride reducing agent in a suitable solvent (see Scheme 1). When either R^1 or R^2 is hydrogen, suitable solvents include protic solvents such as ethanol, and sodium borohydride is an appropriate reducing agent as exemplified by Example 36 herein. When neither R^1 or R^2 are hydrogen, tetrahydrofuran/ dichloromethane is a suitable solvent system and sodium triacetoxyborohydride is a suitable reducing agent.
- 25 In such reactions the use of a salt form of HNR^1R^2 , such as the hydrochloride is preferable, and an auxiliary base, to aid solubility of the HNR^1R^2 salt, such as triethylamine may optionally be added along with acetic acid, as exemplified by Example 25 herein.

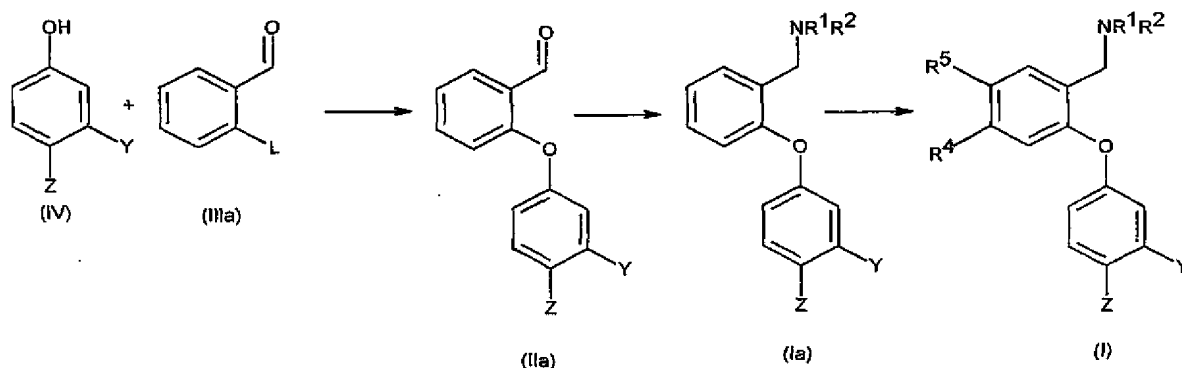
SCHEME 1



- Compounds of formula (II) may be prepared in turn from the coupling of compounds of general formula (IV) with aldehyde compounds of general formula (III), wherein L is a suitable leaving group such as halogen (F, Cl, Br or I) or a sulfonate ester such as trifluoromethanesulfonate or methanesulfonate, preferably L is F or Cl. Such coupling reaction may be accomplished by techniques known in the art, such as via reaction with potassium carbonate in a suitable solvent such as dimethylformamide under appropriate reaction conditions such as elevated temperature and in an inert atmosphere.
- Thus according to a further aspect, the invention provides a process for preparing compounds of general formula (I) from compounds of the general formula (II).

- Alternatively, R⁴ and/or R⁵ may be introduced after ether coupling (see Scheme 2). Compounds of general formula (I) may be prepared from compounds of general formula (Ia), i.e. compounds of general formula (I) where R⁴ and R⁵ are hydrogen. Compounds of general formula (Ia) may be prepared from (IIa) in an analogous fashion to the preparation of (I) from (II) (see Scheme 1), while compounds of general formula (IIa) may be prepared from (IV) and (IIIa) in an analogous fashion to the preparation of (II) (see Scheme 1).

SCHEME 2



Thus according to a further aspect, the invention provides a process for preparing compounds of general formula (I) from compounds of the general formula (Ia).

5

Methodologies for introducing R⁴ and/or R⁵ into compounds of formula (Ia) include:

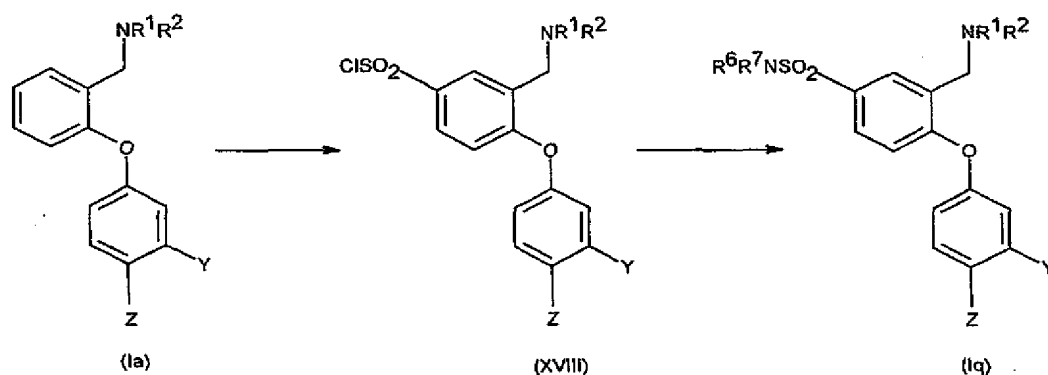
- i) Where R⁴/R⁵ are halogen, by reaction of (Ia) with a suitable halogenating agent in an inert solvent which does not adversely affect the reaction. Suitable halogenating agents include trifluoromethanesulfonic acid and *N*-iodosuccinimide and suitable inert solvents include dichloromethane.
- ii) Where R⁴/R⁵ are -NO₂, by reaction of (Ia) with a suitable nitrating agent, such as an alkali metal nitrate, in a solvent which does not adversely affect the reaction at, or below, room temperature. Suitable nitrating agents include trifluoromethanesulfonic acid/ potassium nitrate and suitable solvents include trifluoroacetic acid.
- iii) Where R⁴/R⁵ is -SO₂NR⁶R⁷ by reaction of an intermediate sulfonyl chloride with the requisite amine of formula HNR⁶R⁷ in a suitable solvent. Suitable solvents include a mixture of water and dichloromethane and the reactions are generally performed at or below room temperature. The intermediate sulfonyl chlorides may be prepared from compounds of formula (Ia) by reaction with chlorosulfonic acid under low temperature conditions in the presence of a solvent which does not adversely affect the reaction, either with or without subsequent treatment with a chlorinating agent such as phosphorus oxychloride, phosphorus pentachloride,

25

oxalyl chloride or thionyl chloride in a solvent which does not adversely affect the reaction. Suitable solvents for the reaction with chlorosulfonic acid include trifluoroacetic acid and a typical reaction temperature is 0 °C. Suitable solvents for the reaction with chlorinating agents include acetonitrile and suitable conditions include at reflux, as illustrated in Example 12 herein.

For example, compounds of formula (Iq), where R^5 is $-\text{SO}_2\text{NR}^6\text{R}^7$, may be prepared via the intermediate sulfonyl chlorides (XVIII) from compounds of formula (Ia) by reaction of (Ia) with chlorosulfonic acid, either with or without subsequent treatment with a chlorinating agent such as phosphorus oxychloride, phosphorus pentachloride, oxalyl chloride or thionyl chloride, followed by reaction with HNR^6R^7 (see scheme 2a). Reaction conditions typically comprise low temperature. The reaction can take place either neat, i.e. in the absence of solvent, or in the presence of an inert solvent which does not adversely affect the reaction. The intermediate sulfonyl chloride (XVII) may be isolated, purified and then reacted with HNR^6R^7 , alternatively it may be generated *in situ*, without isolation, and then reacted with HNR^6R^7 .

SCHEME 2a



Thus according to a further aspect, the invention provides a process for preparing compounds of general formula (I) from compounds of the general formula (II). In a preferred embodiment, there is provided a process for preparing compounds of formula (Iq) by reacting compounds of formula (Ia) in a suitable solvent, with chlorosulfonic acid, either with or without subsequent treatment with a chlorinating agent such as phosphorus oxychloride, phosphorus pentachloride, oxalyl chloride or thionyl chloride, to give compounds of formula (XVIII) followed by reaction with HNR^6R^7 to give compounds

of formula (Iq). Preferably compounds of formula (XVIII) are generated *in situ* and reacted with HNR^6R^7 without isolation.

Alternatively, compounds of general formula (I) having a particular R^4/R^5 substituent may
5 be converted into other compounds of formula (I) using known techniques. For example:

- 10 i) When R^4/R^5 is halogen such as chloro, bromo or iodo, it may be converted to cyano via reaction with a cyanide salt in the presence of a Pd(0) or (II) catalyst in a high boiling solvent at elevated temperatures. Suitable Pd catalysts include palladium tetrakis(triphenylphosphine), suitable cyanide salts include Zn(CN)_2 and suitable high boiling solvents which do not adversely affect the reaction include dimethylformamide as exemplified by Example 78 herein;
- 15 ii) When R^4/R^5 is halogen such as chloro, bromo or iodo, it may be converted to the corresponding ester $-\text{CO}_2\text{R}$ by treatment with carbon monoxide at high pressure with a Pd(0) or (II) catalyst, in an alcohol solvent (ROH wherein R is $\text{C}_1 - \text{C}_4$ alkyl), in the presence of a base at elevated temperatures. For example the reaction may be carried out at pressures in the region of about 100 p.s.i, whilst
20 suitable Pd catalysts include dichlorobis(triphenylphosphine) palladium (II), suitable bases include triethylamine and suitable alcohol solvents include methanol as exemplified by Preparation 50 herein;
- 25 iii) When R^4/R^5 is nitro, it may be reduced to the corresponding $-\text{NH}_2$ group via treatment with a reducing agent in a protic solvent at, or above, room temperature. Suitable reducing agents include iron powder / calcium chloride, suitable protic solvents include aqueous ethanol and a typical reaction temperature is from about 70°C to about 100°C , preferably about 90°C , as exemplified by Example 103 herein;
- 30 iv) When R^4/R^5 is $-\text{NH}_2$, it may be converted to the corresponding $-\text{NHSO}_2\text{R}^9$ group by reaction with a sulfonylating agent in the presence of a base in an inert solvent which does not adversely affect the reaction at, or below, room temperature. Suitable sulfonylating agents include methanesulfonyl chloride, suitable bases include triethylamine and suitable inert solvents include dichloromethane as
35 exemplified by Example 128 herein;

- v) When R^4/R^5 is a $-NHSO_2R^9$ group, it may be converted to the corresponding $-NR^9SO_2R^9$ group via treatment with an alkylating agent and a base in a suitable inert solvent. Examples of suitable alkylating agents include methyl iodide, suitable bases include potassium carbonate and suitable inert solvents include acetonitrile, as exemplified by Preparation 88 herein;
- vi) When R^4/R^5 is a nitrile $-CN$, it may be converted to the corresponding $-C(O)NH_2$ group by hydrolysis under basic, oxidative or acid conditions. Basic hydrolysis is preferably conducted with a hydroxide salt such as potassium hydroxide in a protic solvent such as *t*-butanol at elevated temperatures, as exemplified in Example 79 herein.
- vii) When R^4/R^5 is an ester $-CO_2R$, it may be reduced to the corresponding alcohol group $-CH_2OH$ via treatment with a hydride reducing agent, such as lithium aluminium hydride, as exemplified by Preparation 69 herein;
- viii) When R^4/R^5 is an ester $-CO_2R$, it may be converted to the corresponding acid $-CO_2H$ by treatment with a suitable hydroxide salt in the presence of water and a suitable co-solvent. Suitable hydroxide salts include lithium hydroxide and suitable co-solvents include tetrahydrofuran, as exemplified by Preparation 55 herein;
- ix) When R^4/R^5 is an acid $-CO_2H$, it may be converted to the corresponding amide $-CONR^6R^7$ by treatment with a coupling agent, a base and an amine HNR^6R^7 in a suitable inert solvent which does not adversely affect the reaction. Suitable coupling agents include 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride in the presence of 1-hydroxybenzotriazole, suitable bases include triethylamine and suitable solvents include dichloromethane, as exemplified by Preparation 59 herein;
- x) When R^4/R^5 is halogen such as chloro, bromo or iodo, it may be converted to an α,β -unsaturated amide, by treatment with acrylamide, a Pd(0) or (II) catalyst and a suitable base, in an inert solvent which does not adversely affect the reaction, at elevated temperatures. Suitable Pd catalysts include palladium (II) acetate in

the presence of tri(*o*-tolyl)phosphine, suitable bases include triethylamine and suitable inert solvents include acetonitrile as exemplified by Example 50 herein;

- xi) When R^4/R^5 is an α,β -unsaturated amide, it may be converted to –
5 $\text{CH}_2\text{CH}_2\text{CO}_2\text{NH}_2$, by treatment with a suitable reducing agent at an appropriate temperature, in a suitable solvent which does not adversely affect the reaction. Suitable reducing agents include samarium diiodide at room temperature and suitable solvents include tetrahydrofuran containing a small amount of water, as exemplified by Example 51 herein;
- 10
- xii) When R^4/R^5 is $-\text{CH}_2\text{OH}$, it may be converted to $-\text{CH}_2\text{NR}^8\text{SO}_2\text{R}^9$ by means of a Mitsunobu reaction at an appropriate temperature, in a suitable solvent which does not adversely affect the reaction. Suitable reagents include diethyl
15 azodicarboxylate, triphenylphosphine and *tert*-butyl methylsulfonylcarbamate, 0°C is a suitable reaction temperature and tetrahydrofuran is a suitable solvent as exemplified by Preparation 72 herein;

Alternatively, compounds of general formula (I) having a particular NR^1R^2 group may be converted into other compounds of general formula (I) having a different NR^1R^2 group.

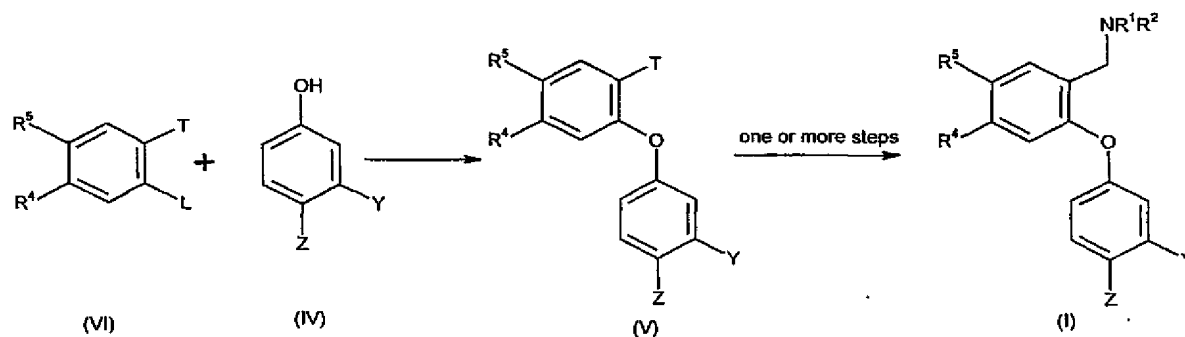
20 For example:

- i) Compounds of formula (Ib) wherein either R^1 or R^2 is hydrogen, can be converted into a compound of formula (Ic) wherein neither R^1 nor R^2 are hydrogen, by
25 reaction of the compound of formula (Ib) with an aldehyde and a hydride reducing agent. Suitable aldehydes include formaldehyde, suitable reducing agents include sodium tri(acetoxy)borohydride and the reaction is preferably conducted in a solvent which does not interfere with the reaction, such as dichloromethane at or below room temperature, as exemplified by Example 12 herein.
- 30
- ii) Compounds of formula (Ib) wherein R^1 or R^2 is hydrogen, can be converted into a compound of formula (Ic) wherein R^1 or R^2 is methyl, by reaction of the
35 compound of formula (Ib) with a formylating agent in a suitable solvent, followed by subsequent reduction of the intermediate *N*-formyl compound with a hydride reducing agent in an inert solvent, preferably at elevated temperature. Suitable

formylating agents include pentafluorophenyl formate (formed from formic acid, pentafluorophenol and dicyclohexylcarbodiimide) and suitable solvents for the formylation include dichloromethane. Suitable reducing agents include borane-tetrahydrofuran complex and suitable inert solvents for the reduction include tetrahydrofuran as exemplified by Example 110 herein.

Alternatively, compounds of general formula (I) may be prepared from compounds of formula V (see Scheme 3) wherein L is as defined for Scheme 1 and T is a group which can be converted into $\text{CH}_2\text{NR}^1\text{R}^2$. Examples of suitable T substituents include: $-\text{CO}_2\text{R}^{10}$, $-\text{CN}$ and $-\text{C}(\text{O})\text{NR}^1\text{R}^2$.

SCHEME 3



Methodologies for converting compounds of formula (V) to (I), include:

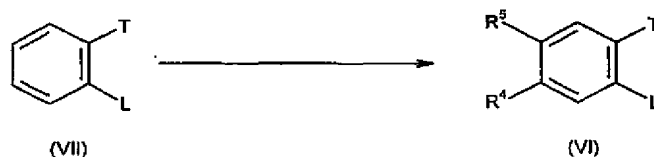
- i) Where T is $-\text{CO}_2\text{R}^{10}$ and R^{10} = methyl or ethyl, by reaction with an amine of general formula NHR^1R^2 to form an amide, followed by reduction to provide an amine.
- ii) Where T = $-\text{CN}$, by reduction to its corresponding amine of formula $-\text{CH}_2\text{NH}_2$.
- iii) Where T = $-\text{C}(\text{O})\text{NR}^1\text{R}^2$, by reduction to provide an amine.

Compounds of general formula (V) may be prepared in turn by the coupling of compounds of general formula (VI) and compounds of the general formula (IV).

Reagents and conditions for such coupling reactions are as previously defined for the coupling of compounds of general formulae (IV) and (III) in Scheme 1.

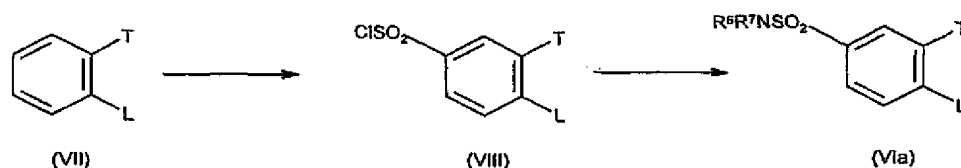
Compounds of general formula (VI) may be prepared in turn from compounds of general formula (VII) (see Scheme 4).

SCHEME 4



Compounds of formula (VI) may be prepared by aromatic electrophilic substitution of compounds of formula (VII) to give compounds of formula (VI) directly. Alternatively compounds of formula (VI) may be prepared in two or more steps; aromatic electrophilic substitution of compounds of formula (VII) to give intermediate compounds which then undergo further reaction to give compounds of formula (VI). The intermediate compounds may be isolated or generated *in situ* without isolation. A preferred route is shown in Scheme 5.

SCHEME 5



Compounds of formula (VII) are reacted with sulfonyl chloride to give compounds of formula (VIII) followed by reaction with NHR^6R^7 to give compounds of formula (VIa).

According to further aspects, the invention provides compounds of formulae (II), (IIa) and (V) as defined above.

Compounds of formulae (III), (IIIa), (IV), (VI) or (VII) are either known and available from commercial sources or are available from commercially available materials using known techniques (see Examples hereinafter).

It will be apparent to those skilled in the art that sensitive functional groups may need to be protected and deprotected during synthesis of a compound of formula I. This may be achieved by conventional techniques, for example as described in 'Protective Groups in Organic Synthesis', 3rd edition, by T W Greene and P G M Wuts, John Wiley and Sons

Inc, 1999. Example 35 provides one example of a protecting group strategy employed in the synthesis of a compound of the present invention.

5 The skilled chemist will appreciate that diaryl ethers may be prepared using a number of synthetic methodologies. For a review of methodologies see J S Sawyer, *Tetrahedron*, 56 (2000) 5045-5065, incorporated herein by reference.

10 The compounds of the invention are useful because they have pharmacological activity in mammals, including humans. More particularly, they are useful in the treatment or prevention of a disorder in which the regulation of monoamine transporter function is implicated. Disease states that may be mentioned include hypertension, depression (e.g. depression in cancer patients, depression in Parkinson's patients, postmyocardial infarction depression, subsyndromal symptomatic depression, depression in infertile women, paediatric depression, major depression, single episode depression, recurrent depression, child abuse induced depression, post partum depression and grumpy old man syndrome), generalized anxiety disorder, phobias (e.g. agoraphobia, social phobia and simple phobias), posttraumatic stress syndrome, avoidant personality disorder, premature ejaculation, eating disorders (e.g. anorexia nervosa and bulimia nervosa), obesity, chemical dependencies (e.g. addictions to alcohol, cocaine, heroin, 15 phenobarbital, nicotine and benzodiazepines), cluster headache, migraine, pain, Alzheimer's disease, obsessive-compulsive disorder, panic disorder, memory disorders (e.g. dementia, amnesic disorders, and age-related cognitive decline (ARCD)), Parkinson's diseases (e.g. dementia in Parkinson's disease, neuroleptic-induced parkinsonism and tardive dyskinesias), endocrine disorders (e.g. hyperprolactinaemia), vasospasm (particularly in the cerebral vasculature), cerebellar ataxia, gastrointestinal tract disorders (involving changes in motility and secretion), negative symptoms of schizophrenia, premenstrual syndrome, fibromyalgia syndrome, stress incontinence, Tourette's syndrome, trichotillomania, kleptomania, male impotence, attention deficit hyperactivity disorder (ADHD), chronic paroxysmal hemicrania, headache (associated with vascular disorders), emotional lability, pathological crying, sleeping disorder 20 (cataplexy) and shock.

Disorders of particular interest include depression, attention deficit hyperactivity disorder, obsessive-compulsive disorder, post-traumatic stress disorder, substance abuse 25 disorders and sexual dysfunction including (in particular) premature ejaculation.

Premature ejaculation may be defined as persistent or recurrent ejaculation before, upon or shortly after penile penetration of a sexual partner. It may also be defined as ejaculation occurring before the individual wishes [see 'The Merck Manual', 16th edition, p 1576, published by Merck Research Laboratories, 1992].

5

Thus, according to further aspects, the invention provides:

- i) a compound of the invention for use as a pharmaceutical;
- 10 ii) the use of a compound of the invention in the manufacture of a medicament for the treatment or prevention of a disorder in which the regulation of monoamine transporter function is implicated, for example depression, attention deficit hyperactivity disorder, obsessive-compulsive disorder, post-traumatic stress disorder, substance abuse disorders or sexual dysfunction including premature
15 ejaculation;
- iii) the use of a compound of the invention in the manufacture of a medicament for the treatment or prevention of premature ejaculation;
- 20 iv) a method of treatment or prevention of depression, attention deficit hyperactivity disorder, obsessive-compulsive disorder, post-traumatic stress disorder, substance abuse disorders or sexual dysfunction including premature ejaculation, which comprises administering a therapeutically effective amount of a compound of the invention to a patient in need of such treatment or prevention;
- 25 v) a method of increasing ejaculatory latency which comprises the administration of an effective amount of a compound of the invention to a male desiring increased ejaculatory latency; and
- 30 vi) a compound of the invention for the treatment or prevention of a disorder in which the regulation of monoamine transporter function is implicated, for example depression, attention deficit hyperactivity disorder, obsessive-compulsive disorder, post-traumatic stress disorder, substance abuse disorders or sexual dysfunction including premature ejaculation.

35

- vii) a compound of the invention for treating premature ejaculation.

It is to be appreciated that all references herein to treatment include curative, palliative and prophylactic treatment.

5

The compounds of the invention may be administered alone or as part of a combination therapy. If a combination of active agents are administered, then they may be administered simultaneously, separately or sequentially. In particular, the compounds of the invention may be combined with the following preferably for the treatment of PE:

10

- i) Alpha-blockers (e.g. phentolamine, doxazosin, tamsulosin, terazosin, prazosin and Example 19 of WO9830560. A possible rationale for alpha-blockers treating premature ejaculation is as follows. Muscular activity of the ejaculatory smooth muscles (vas deferens, seminal vesicles and urethra) are controlled by the sympathetic nervous system through the release of noradrenalin. Noradrenalin acts on the alpha 1 adrenoreceptors, stimulating muscle contractions, leading to seminal emission and subsequently ejaculation. Blocking these receptors will therefore inhibit ejaculation.

15

- 20 ii) Apomorphine - teachings on the use of apomorphine as a pharmaceutical may be found in US-A-5945117.

- iii) Dopamine D2 agonists (e.g. Premipruxal, Pharmacia Upjohn compound number PNU95666).

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- iv) Melanocortin receptor agonists (e.g. Melanotan II).

- v) PGE1 receptor agonists (e.g. alprostadil).

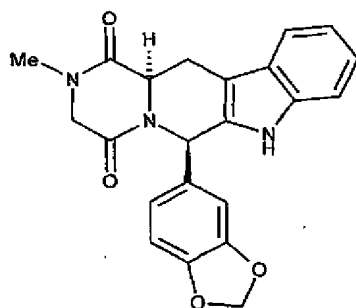
- 30 vi) Mono amine transport inhibitors, particularly Noradrenaline Re-uptake Inhibitors (NRIs) (e.g. Reboxetine), other Serotonin Re-uptake Inhibitors (SRIs) (e.g. paroxetine) or Dopamine Re-uptake Inhibitors (DRIs).

- 35 vii) 5-HT3 antagonists (e.g. ondansetron and granisetron). A possible rationale for 5-HT3 antagonists treating premature ejaculation is as follows. 5-HT3 receptors,

present in the lumen of the posterior portion of the urethra, are stimulated by 5-HT in the semen during seminal emission, leading to a sensitisation of the spinal reflex pathway which leads to ejaculation. Therefore, an antagonist would prevent this sensitisation and thus delay ejaculation.

5

- viii) PDE inhibitors such as PDE2 (e.g. erythro-9-(2-hydroxyl-3-nonyl)-adenine) and Example 100 of EP 0771799-incorporated herein by reference) and in particular a PDE5 inhibitor (e.g. sildenafil, 1-[[3-(3,4-dihydro-5-methyl-4-oxo-7-propylimidazo[5,1-f]-as-triazin-2-yl)-4-ethoxyphenyl]sulfonyl]-4-ethylpiperazine i.e. vardenafil / Bayer BA 38-9456 or IC351 (see structure below, Icos Lilly)). A possible rationale for PDE inhibitors treating premature ejaculation is as follows. c
- 10 AMP and CGMP levels in the ejaculatory smooth muscles regulate muscle tone of these ejaculatory muscles and so delay ejaculation.



IC351 (Icos Lilly)

15

- ix) Potassium channel openers.
- x) P2X purinergic receptor antagonists.
- 20 xi) Endothelin receptor antagonists

For human use the compounds of the invention can be administered alone but in human therapy will generally be administered in admixture with a suitable pharmaceutical excipient, diluent or carrier selected with regard to the intended route of administration

25 and standard pharmaceutical practice.

For example, the compounds of the invention, can be administered orally, buccally or sublingually in the form of tablets, capsules (including soft gel capsules), ovules, elixirs, solutions or suspensions, which may contain flavouring or colouring agents, for

immediate-, delayed-, modified-, sustained-, dual-, controlled-release or pulsatile delivery applications. The compounds of the invention may also be administered via intracavernosal injection. The compounds of the invention may also be administered via fast dispersing or fast dissolving dosage forms.

5

Such tablets may contain excipients such as microcrystalline cellulose, lactose, sodium citrate, calcium carbonate, dibasic calcium phosphate, glycine, and starch (preferably corn, potato or tapioca starch), disintegrants such as sodium starch glycolate, croscarmellose sodium and certain complex silicates, and granulation binders such as polyvinylpyrrolidone, hydroxypropylmethylcellulose (HPMC), hydroxypropylcellulose (HPC), sucrose, gelatin and acacia. Additionally, lubricating agents such as magnesium stearate, stearic acid, glyceryl behenate and talc may be included.

10

Solid compositions of a similar type may also be employed as fillers in gelatin capsules. Preferred excipients in this regard include lactose, starch, a cellulose, milk sugar or high molecular weight polyethylene glycols. For aqueous suspensions and/or elixirs, the compounds of the invention, and their pharmaceutically acceptable salts, may be combined with various sweetening or flavouring agents, colouring matter or dyes, with emulsifying and/or suspending agents and with diluents such as water, ethanol, propylene glycol and glycerin, and combinations thereof.

15

20

Modified release and pulsatile release dosage forms may contain excipients such as those detailed for immediate release dosage forms together with additional excipients that act as release rate modifiers, these being coated on and/or included in the body of the device. Release rate modifiers include, but are not exclusively limited to, hydroxypropylmethyl cellulose, methyl cellulose, sodium carboxymethylcellulose, ethyl cellulose, cellulose acetate, polyethylene oxide, Xanthan gum, Carbomer, ammonio methacrylate copolymer, hydrogenated castor oil, carnauba wax, paraffin wax, cellulose acetate phthalate, hydroxypropylmethyl cellulose phthalate, methacrylic acid copolymer and mixtures thereof. Modified release and pulsatile release dosage forms may contain one or a combination of release rate modifying excipients. Release rate modifying excipients may be present both within the dosage form i.e. within the matrix, and/or on the dosage form, i.e. upon the surface or coating.

25

30

Fast dispersing or dissolving dosage formulations (FDDFs) may contain the following ingredients: aspartame, acesulfame potassium, citric acid, croscarmellose sodium, crospovidone, diascorbic acid, ethyl acrylate, ethyl cellulose, gelatin, hydroxypropylmethyl cellulose, magnesium stearate, mannitol, methyl methacrylate, mint
5 flavouring, polyethylene glycol, fumed silica, silicon dioxide, sodium starch glycolate, sodium stearyl fumarate, sorbitol, xylitol. The terms dispersing or dissolving as used herein to describe FDDFs are dependent upon the solubility of the drug substance used i.e. where the drug substance is insoluble a fast dispersing dosage form can be prepared and where the drug substance is soluble a fast dissolving dosage form can be
10 prepared.

The compounds of the invention can also be administered parenterally, for example, intravenously, intra-arterially, intraperitoneally, intrathecally, intraventricularly, intraurethrally, intrasternally, intracranially, intramuscularly or subcutaneously, or they
15 may be administered by infusion techniques. For such parenteral administration they are best used in the form of a sterile aqueous solution which may contain other substances, for example, enough salts or glucose to make the solution isotonic with blood. The aqueous solutions should be suitably buffered (preferably to a pH of from 3 to 9), if necessary. The preparation of suitable parenteral formulations under sterile
20 conditions is readily accomplished by standard pharmaceutical techniques well known to those skilled in the art.

The following dosage levels and other dosage levels herein are for the average human subject having a weight range of about 65 to 70 kg. The skilled person will readily be
25 able to determine the dosage levels required for a subject whose weight falls outside this range, such as children and the elderly.

For oral and parenteral administration to human patients, the daily dosage level of the compounds of the invention or salts or solvates thereof will usually be from 10 to 500 mg
30 (in single or divided doses).

Thus, for example, tablets or capsules of the compounds of the invention may contain from 5 mg to 250 mg of active compound for administration singly or two or more at a time, as appropriate. The physician in any event will determine the actual dosage which
35 will be most suitable for any individual patient and it will vary with the age, weight and

response of the particular patient. The above dosages are exemplary of the average case. There can, of course, be individual instances where higher or lower dosage ranges are merited and such are within the scope of this invention. The skilled person will also appreciate that, in the treatment of certain conditions (including PE),

- 5 compounds of the invention may be taken as a single dose on an "as required" basis (i.e. as needed or desired).

Example Tablet Formulation

- 10 In general a tablet formulation could typically contain between about 0.01mg and 500mg of a compound of the invention whilst tablet fill weights may range from 50mg to 1000mg. An example formulation for a 10mg tablet is illustrated:

	<u>Ingredient</u>	<u>%w/w</u>
	Compound of the invention	10.000*
15	Lactose	64.125
	Starch	21.375
	Croscarmellose Sodium	3.000
	Magnesium Stearate	1.500

- 20 * This quantity is typically adjusted in accordance with drug activity.

- The compounds of the invention can also be administered intranasally or by inhalation and are conveniently delivered in the form of a dry powder inhaler or an aerosol spray presentation from a pressurised container, pump, spray or nebulizer with the use of a
- 25 suitable propellant, e.g. dichlorodifluoromethane, trichlorofluoromethane, dichlorotetrafluoro-ethane, a hydrofluoroalkane such as 1,1,1,2-tetrafluoroethane (HFA 134A [trade mark]) or 1,1,1,2,3,3,3-heptafluoropropane (HFA 227EA [trade mark]), carbon dioxide or other suitable gas. In the case of a pressurised aerosol, the dosage unit may be determined by providing a valve to deliver a metered amount. The pressurised
- 30 container, pump, spray or nebulizer may contain a solution or suspension of the active compound, e.g. using a mixture of ethanol and the propellant as the solvent, which may additionally contain a lubricant, e.g. sorbitan trioleate. Capsules and cartridges (made, for example, from gelatin) for use in an inhaler or insufflator may be formulated to contain a powder mix of a compound of the invention and a suitable powder base such
- 35 as lactose or starch.

Aerosol or dry powder formulations are preferably arranged so that each metered dose or "puff" contains from 1 to 50 mg of a compound of the invention for delivery to the patient. The overall daily dose with an aerosol will be in the range of from 1 to 50 mg
5 which may be administered in a single dose or, more usually, in divided doses throughout the day.

The compounds of the invention may also be formulated for delivery via an atomiser. Formulations for atomiser devices may contain the following ingredients as solubilisers,
10 emulsifiers or suspending agents: water, ethanol, glycerol, propylene glycol, low molecular weight polyethylene glycols, sodium chloride, fluorocarbons, polyethylene glycol ethers, sorbitan trioleate, oleic acid.

Alternatively, the compounds of the invention can be administered in the form of a
15 suppository or pessary, or they may be applied topically in the form of a gel, hydrogel, lotion, solution, cream, ointment or dusting powder. The compounds of the invention may also be dermally or transdermally administered, for example, by the use of a skin patch. They may also be administered by the ocular, pulmonary or rectal routes.

20 For ophthalmic use, the compounds can be formulated as micronized suspensions in isotonic, pH adjusted, sterile saline, or, preferably, as solutions in isotonic, pH adjusted, sterile saline, optionally in combination with a preservative such as a benzylalkonium chloride. Alternatively, they may be formulated in an ointment such as petrolatum.

25 For application topically to the skin, the compounds of the invention can be formulated as a suitable ointment containing the active compound suspended or dissolved in, for example, a mixture with one or more of the following: mineral oil, liquid petrolatum, white petrolatum, propylene glycol, polyoxyethylene polyoxypropylene compound, emulsifying wax and water. Alternatively, they can be formulated as a suitable lotion or cream,
30 suspended or dissolved in, for example, a mixture of one or more of the following: mineral oil, sorbitan monostearate, a polyethylene glycol, liquid paraffin, polysorbate 60, cetyl esters, wax, cetearyl alcohol, 2-octyldodecanol, benzyl alcohol and water.

The compounds of the invention may also be used in combination with a cyclodextrin.
35 Cyclodextrins are known to form inclusion and non-inclusion complexes with drug

molecules. Formation of a drug-cyclodextrin complex may modify the solubility, dissolution rate, bioavailability and/or stability property of a drug molecule. Drug-cyclodextrin complexes are generally useful for most dosage forms and administration routes. As an alternative to direct complexation with the drug the cyclodextrin may be used as an auxiliary additive, e.g. as a carrier, diluent or solubiliser. Alpha-, beta- and gamma-cyclodextrins are most commonly used and suitable examples are described in WO-A-91/11172, WO-A-94/02518 and WO-A-98/55148.

For oral or parenteral administration to human patients the daily dosage levels of compounds of the invention will be from 0.01 to 30 mg/kg (in single or divided doses) and preferably will be in the range 0.01 to 5 mg/kg. Thus tablets will contain 1mg to 0.4g of compound for administration singly or two or more at a time, as appropriate. The physician will in any event determine the actual dosage which will be most suitable for any particular patient and it will vary with the age, weight and response of the particular patient. The above dosages are, of course only exemplary of the average case and there may be instances where higher or lower doses are merited, and such are within the scope of the invention.

Oral administration is preferred. Preferably, administration takes place shortly before an effect is required.

For veterinary use, a compound of the invention is administered as a suitably acceptable formulation in accordance with normal veterinary practice and the veterinary surgeon will determine the dosing regimen and route of administration which will be most appropriate for a particular animal.

Thus according to a further aspect, the invention provides a pharmaceutical formulation containing a compound of the invention and a pharmaceutically acceptable adjuvant, diluent or carrier.

The invention is illustrated by the following non-limiting examples in which the following abbreviations and definitions are used:

Arbocel®	filter agent
br	broad

Boc	<i>tert</i> -butoxycarbonyl
CDI	carbonyldiimidazole
δ	chemical shift
d	doublet
Δ	heat
DCCI	dicyclohexylcarbodiimide
DCM	dichloromethane
DMF	<i>N,N</i> -dimethylformamide
DMSO	dimethylsulfoxide
ES ⁺	electrospray ionisation positive scan
ES ⁻	electrospray ionisation negative scan
Ex	Example
h	hours
HOBt	1-hydroxybenzotriazole
HPLC	high pressure liquid chromatography
m/z	mass spectrum peak
min	minutes
MS	mass spectrum
NMR	nuclear magnetic resonance
Prec	precursor
Prep	preparation
q	quartet
s	singlet
t	triplet
Tf	trifluoromethanesulfonyl
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TLC	thin layer chromatography
TS ⁺	thermospray ionisation positive scan
WSCDI	1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride

¹H Nuclear magnetic resonance (NMR) spectra were in all cases consistent with the proposed structures. Characteristic chemical shifts (δ) are given in parts-per-million downfield from tetramethylsilane using conventional abbreviations for designation of major peaks: e.g. s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad.

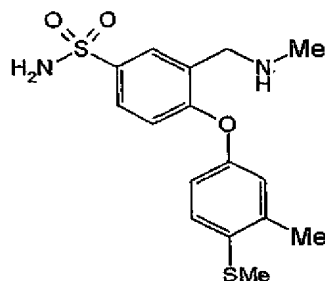
The following abbreviations have been used for common solvents: CDCl_3 , deuteriochloroform; DMSO, dimethylsulfoxide. The abbreviation psi means pounds per square inch and LRMS means low resolution mass spectrometry. Where thin layer chromatography (TLC) has been used it refers to silica gel TLC using silica gel 60 F₂₅₄ plates, R_f is the distance travelled by a compound divided by the distance travelled by the solvent front on a TLC plate. Melting points were determined using a Perkin Elmer DSC7 at a heating rate of 20°C/minute).

Where indicated, compounds were characterised as their hydrochloride salts. A typical procedure for formation of hydrochloride salts is given in Example 12. The procedure can be carried out with other solvents e.g. diethyl ether or DCM.

Commercial starting materials were obtained from Aldrich Chemical Co, Lancaster Synthesis Ltd or Acros Organics.

EXAMPLE 1

3-[(Methylamino)methyl]-4-[3-methyl-4-methylsulfonyl]phenoxy]-benzenesulfonamide

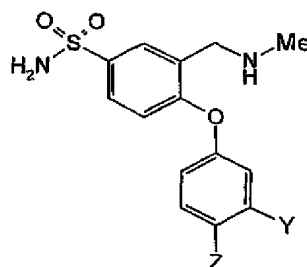


The amide of Preparation 8 (760 mg, 2.07 mmol) was slurried in THF (10 mL) and the resulting suspension was treated with borane.tetrahydrofuran complex (1M solution in THF, 6.22 mL, 6.22 mmol) at room temperature. The resulting solution was heated at reflux for 5 hours under an atmosphere of dry nitrogen. The reaction was cooled to room temperature and treated cautiously with 6M HCl solution (6 mL). The resulting mixture was heated at reflux for 30 min. After cooling to room temperature the mixture was diluted with water (10 mL) and basified by cautious addition of potassium carbonate solid. The aqueous layer was extracted with EtOAc (20 mL) which gave a precipitate in the organic layer, and the aqueous layer was further extracted with DCM (2 x 20 mL). The EtOAc fraction was washed with 2M NaOH (20 mL) giving a clear two-phase separation and the basic layer was extracted with DCM (4 x 25 mL). All the organic fractions were combined and washed with brine (20 mL), dried (MgSO_4) and evaporated

to a colourless oil. Purification by flash chromatography [SiO_2 ; 95:5:0.5 to 90:10:1 (EtOAc/ MeOH/ 880 NH_3)] afforded a white powder of the desired amine (646 mg, 89%). δ_{H} (300 MHz, d_6 -DMSO) 2.26 (3H, d), 2.32 (3H, d), 2.45 (3H, d), 3.75 (2H, d), 6.90 (3H, m), 7.25 (3H, br), 7.67 (1H, t) 7.98 (1H, d); MS m/z (TS^+) 353 (MH^+).

5

Compounds of formula Id, i.e. compounds of general formula I where R^1 is methyl, R^2 is hydrogen and R^5 is $-\text{SO}_2\text{NH}_2$, shown in Table 1 were prepared in an analogous fashion to Example 1 from the precursors indicated.

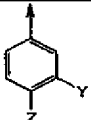
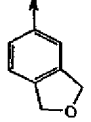
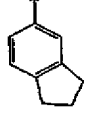
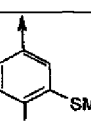
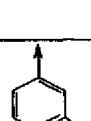
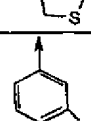


(Id)

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Table 1

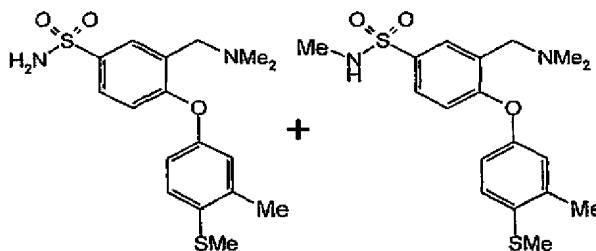
Example	Precursor		data
2	Prep 9		HCl salt: δ_{H} (CD_3OD , 400 MHz) 2.80 (3H, s), 3.42 (2H, m), 4.41 (2H, s), 6.86-7.00 (2H, m), 7.09 (1H, s), 7.23 (1H, d), 7.90 (1H, d), 8.05 (1H, s); MS m/z (TS^+) 351 (MH^+)
3	Prep 12		HCl salt: δ_{H} (CD_3OD , 300 MHz) 2.54 (3H, s), 2.82 (3H, s), 4.43 (2H, s), 7.00 (1H, d), 7.20 (1H, d), 7.34 (1H, s), 7.42 (1H, d), 7.95 (1H, d), 8.11 (1H, s); MS m/z (TS^+) 373 (MH^+)
4	Prep 11		HCl salt: δ_{H} (CD_3OD , 400 MHz) 2.45 (3H, s), 2.73 (3H, s), 5.44 (2H, s), 6.97 (3H, m), 7.42 (1H, m), 7.89 (1H, m), 8.03 (1H, s); MS m/z (ES^+) 357 (MH^+)
5	Prep 10		HCl salt: δ_{H} (CD_3OD , 400 MHz) 2.79 (3H, s), 3.18 (2H, m), 4.38 (2H, s), 4.41 (2H, m), 6.68 (2H, m), 6.97 (1H, d), 7.13 (1H, d), 7.91 (1H, d), 8.03 (1H, s); MS m/z (TS^+) 367 (MH^+)
6	Prep 13		HCl salt: δ_{H} (CD_3OD , 400 MHz) 2.78 (3H, s), 3.15 (2H, m), 4.38 (4H, m), 6.79 (1H, d), 6.85 (3H, m), 7.84 (1H, d), 8.00 (1H, s); MS m/z (ES^+) 367 (MH^+)

Example	Precursor		data
7	Prep 14		HCl salt: δ_H (CD ₃ OD, 400 MHz) 2.81 (3H, s), 4.43 (2H, s), 5.09 (4H, s), 6.93 (1H, d), 7.12 (2H, s+d), 7.40 (1H, d), 7.90 (1H, d), 8.08 (1H, s); MS m/z (TS ⁺) 335 (MH ⁺)
8	Prep 15		HCl salt: δ_H (CD ₃ OD, 400 MHz) 2.16 (2H, m), 2.80 (3H, s), 2.92 (4H, t), 4.40 (2H, s), 6.86 (1H, d), 6.94 (1H, d), 7.03 (1H, s), 7.30 (1H, d), 7.88 (1H, d), 8.03 (1H, s); MS m/z (TS ⁺) 333 (MH ⁺)
9	Prep 16		HCl salt: δ_H (CD ₃ OD, 400 MHz) 2.32 (3H, s), 2.43 (3H, s), 2.81 (3H, s), 4.41 (2H, s), 6.84 (1H, d), 6.91 (1H, d), 7.06 (1H, s), 7.24 (1H, d), 7.89 (1H, d), 8.05 (1H, s); MS m/z (ES ⁺) 352 (MH ⁺)
10	Prep 17		HCl salt: δ_H (CD ₃ OD, 400 MHz) 2.78 (3H, s), 4.21 (4H, s), 4.39 (2H, s), 6.89 (1H, d), 7.01 (1H, d), 7.08 (1H, s), 7.38 (1H, d), 7.85 (1H, d), 8.02 (1H, s); MS m/z (TS ⁺) 351 (MH ⁺)
11	Prep 18		δ_H (CD ₃ OD, 400 MHz) 2.76 (3H, s), 3.30 (2H, m), 3.42 (2H, m), 4.33 (2H, s), 6.90 (1H, d), 6.94 (1H, d), 7.00 (1H, s), 7.29 (2H, d), 7.89 (1H, d), 8.04 (1H, s); MS m/z (ES ⁺) 351 (MH ⁺), (ES ⁻) 349 (M-H ⁺)

EXAMPLES 12 and 13

3-[(Dimethylamino)methyl]-4-[3-methyl-4-(methylsulfanyl)phenoxy]-benzenesulfonamide
(Example 12) and 3-[(dimethylamino)methyl]-N-methyl-4-[3-methyl-4-

5 (methylsulfanyl)phenoxy]benzenesulfonamide (Example 13)



Formaldehyde (37% aq. solution, 282 μ L, 3.76 mmol) was added to a suspension of the secondary amine from Example 1 (409 mg, 1.16 mmol) in DCM (20 mL) at room temperature under nitrogen. The resulting mixture was stirred for 15 minutes before the addition of sodium triacetoxyborohydride (984 mg, 4.64 mmol). The resulting reaction mixture was stirred for 5 hours before being basified with saturated NaHCO₃ solution (10 mL) and extracted with DCM (3 \times 20 mL). The organic layers were washed with brine (10

- mL), dried (MgSO_4) and evaporated to a yellow oil. This was purified by HPLC (Phenomenex Luna C_{18} 75 \times 4.6 mm column, CH_3CN , H_2O , TFA). Fractions containing the major product were evaporated and the residue was treated with sat. NaHCO_3 solution (5 mL), and extracted with DCM (3 \times 30 mL). The combined organic fractions
- 5 were washed with brine (30 mL), dried (MgSO_4) and evaporated to give a white foam (155 mg, 36%) of Example 12; δ_{H} (300 MHz, CDCl_3) 2.30 (6H, s), 2.35 (3H, s), 2.48 (3H, s), 3.60 (2H, s), 6.83 (3H, m), 7.20 (1H, m), 7.28 (2H, s), 7.74 (1H, d), 8.08 (1H, s); MS m/z (TS+) 367 (MH^+).
- 10 A minor product was also obtained after HPLC purification. The relevant fractions were evaporated and the residue was treated with sat. NaHCO_3 solution (5 mL), and extracted with DCM (2 \times 30 mL). The combined organic fractions were washed with brine (30 mL), dried (MgSO_4) and evaporated to a gum. This was taken up in DCM (5 mL), treated with 1M ethereal HCl (2 mL) and evaporated to give a white powder (39 mg, 9%) of Example
- 15 13; HCl salt: δ_{H} (CDCl_3 , 300 MHz) 2.30 (6H, s), 2.35 (3H, s), 2.48 (3H, s), 3.60 (2H, s), 6.83 (3H, m), 7.20 (1H, m), 7.28 (2H, s), 7.74 (1H, d), 8.08 (1H, s); MS m/z (TS+) 381 (MH^+).
- In a repeat reaction, using 1 equivalent of formaldehyde to the amine of Example 1,
- 20 Example 12 was obtained in 78% yield after column chromatography [SiO_2 ; 95:5:0.5 to 90:10:1 (EtOAc/ MeOH/ 880 NH_3)]. This was taken up in EtOAc and converted to the HCl salt by the addition of 1M ethereal HCl. The resulting precipitate was filtered and dried *in vacuo* to give Example 12 HCl salt; m.p. 188°C.
- 25 Alternatively, Example 12 can also be formed from the amine of Example 1 by the method of Example 110.

Example 12 was also prepared as follows.

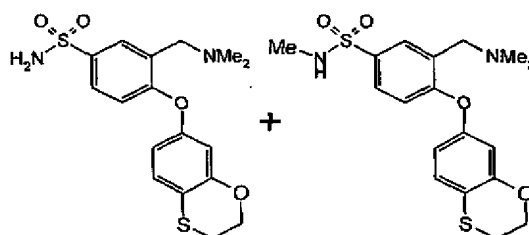
- 30 A solution of the hydrochloride salt from Example 94 (20 g) in trifluoroacetic acid (100 mL) was slowly added to a solution of chlorosulfonic acid (72 g) keeping the temperature between 0 and 5 °C. After 1 h the reaction mixture was quenched slowly into water (200 mL), at 0-20 °C. The mixture was then extracted with dichloromethane (200 mL) and separated. The aqueous layer was then extracted with dichloromethane (60 mL) and
- 35 separated. The combined organic layers were washed with water (200 mL). The layers

were separated and the dichloromethane removed *in vacuo* to give a solid. Acetonitrile (240 mL) was added and to this slurry was added phosphorus oxychloride (28.8 mL). The solution was then heated at reflux overnight. The reaction mixture was cooled to room temperature and quenched into a stirred mixture of ammonia (90 mL),

- 5 dichloromethane (240 mL) and water (100 mL), keeping the temperature between 0 °C and 10 °C. The mixture was adjusted with ammonia (if necessary) to greater than pH8. After 15 mins the reaction mixture was allowed to warm to room temperature and the layers separated. The organic layer was concentrated *in vacuo* to give a thick brown oil. This was dissolved in acetone (100 mL) and slurried with carbon (Norit SX plus, 50% w/w) filtered and treated with another charge of carbon (Norit SX plus, 50%w/w). This
10 mixture was again filtered and the solution concentrated, replacing with water (200 mL). The slurry was granulated, filtered and vacuum dried overnight to give the title product as a creamy white solid (yield 40%).

15 EXAMPLES 14 and 15

4-(2,3-Dihydro-1,4-benzoxathiin-7-yloxy)-3-[(dimethylamino)methyl]-benzenesulfonamide
and 4-(2,3-dihydro-1,4-benzoxathiin-7-yloxy)-3-[(dimethylamino)methyl]-N-
methylbenzenesulfonamide



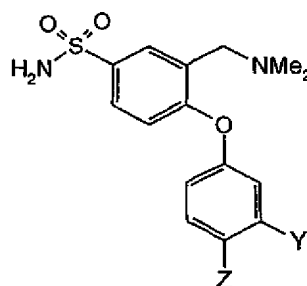
- 20 These compounds were formed in an analogous fashion to Examples 12 and 13 starting from the secondary amine of Example 5.

EXAMPLE 14. HCl salt: δ_H (CD₃OD, 400 MHz) 2.97 (6H, s), 3.18 (2H, m), 4.42 (2H, m), 4.52 (2H, s), 6.68 (2H, d), 6.99 (1H, d), 7.14 (1H, d), 7.94 (1H, d), 8.07 (1H, s); MS *m/z* (ES⁺) 381 (MH⁺).

- 25 EXAMPLE 15. HCl salt: δ_H (CD₃OD, 400 MHz) 2.56 (3H, s), 2.80 (6H, s), 3.17 (2H, m), 4.35 (2H, s), 4.41 (2H, m), 6.68 (2H, m), 6.98 (1H, d), 7.13 (1H, d), 7.81 (1H, d), 8.00 (1H, s); MS *m/z* (ES⁺) 395 (MH⁺).

- Compounds of formula Ie, i.e. compounds of general formula I where R¹ and R² are
30 methyl and R⁵ is -SO₂NH₂, shown in Table 2 were prepared according to Example 12

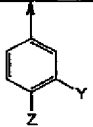
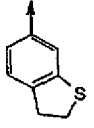
from the precursors indicated. The *N*-methyl sulfonamides analogous to Example 13 were not isolated in these reactions and HPLC purification was not required.

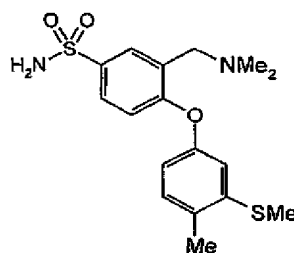


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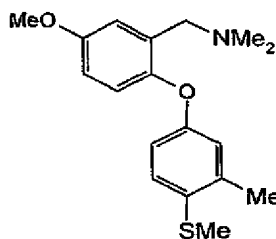
Table 2

Example	Precursor		data
16	Example 2		HCl salt: δ_H (CD ₃ OD, 400 MHz) 2.98 (6H, s), 3.41 (2H, m), 4.58 (2H, s), 6.95 (2H, m), 7.08 (1H, s), 7.25 (1H, d), 7.95 (1H, d), 8.05 (1H, s); MS <i>m/z</i> (ES ⁺) 365 (MH ⁺)
17	Example 3		HCl salt: δ_H (CD ₃ OD, 300 MHz) 2.54 (3H, s), 2.98 (6H, s), 4.53 (2H, s), 7.01 (1H, d), 7.20 (1H, dd), 7.33 (1H, s), 7.42 (1H, d), 7.99 (1H, d), 8.04 (1H, s); MS <i>m/z</i> (TS ⁺) 387 (MH ⁺)
18	Example 4		HCl salt: δ_H (CD ₃ OD, 400 MHz) 2.43 (3H, s), 2.88 (6H, s), 4.42 (2H, s), 6.99 (3H, m), 7.42 (1H, t), 7.92 (1H, d), 8.06 (1H, s); MS <i>m/z</i> (ES ⁺) 371 (MH ⁺)
19	Example 6		HCl salt: δ_H (CD ₃ OD, 400 MHz) 2.89 (3H, s), 3.17 (2H, m), 4.39 (2H, m), 4.47 (2H, s), 6.78 (1H, d), 6.87 (3H, m), 7.89 (1H, d), 8.01 (1H, s); MS <i>m/z</i> (TS ⁺) 367 (MH ⁺)
20	Example 7		TFA salt: δ_H (CDCl ₃ , 400 MHz) 2.22 (6H, s), 3.60 (2H, t), 5.05 (4H, d), 6.75-6.90 (3H, m), 7.20 (1H, d), 7.60 (1H, m), 8.00 (1H, m); MS <i>m/z</i> 349 (MH ⁺)
21	Example 8		HCl salt: δ_H (CD ₃ OD, 400 MHz) 2.10 (2H, m), 2.85-3.00 (10H, m), 4.30 (1H, brs), 4.50 (2H, s), 6.80-6.95 (2H, m), 7.05 (1H, s), 7.25 (1H, d), 7.80 (1H, d), 8.10 (1H, s); MS <i>m/z</i> (ES ⁺) 347 (MH ⁺)
22	Example 10		HCl salt: δ_H (CD ₃ OD, 400 MHz) 2.93 (6H, s), 4.21 (4H, s), 4.50 (2H, s), 6.91 (1H, d), 7.02 (1H, d), 7.09 (1H, s), 7.37 (1H, d), 7.91 (1H, d), 8.05 (1H, s); MS <i>m/z</i> (TS ⁺) 365 (MH ⁺)

Example	Precursor		data
23	Example 11		HCl salt: δ_H (DMSO- d_6 , 400 MHz) 2.76 (6H, s), 3.21 (2H, t), 3.38 (2H, t), 4.39 (2H, s), 6.80 (1H, d), 6.86 (1H, d), 7.10 (1H, s), 7.28 (3H, m), 7.80 (1H, d), 8.06 (1H, s), 10.23 (1H, br); MS m/z (TS ⁺) 365 (MH ⁺)

EXAMPLE 24**3-[(Dimethylamino)methyl]-4-[4-methyl-3-(methylsulfanyl)phenoxy]-benzenesulfonamide**

- 5 The title compound was prepared from the secondary amine of Example 9 by the method of Example 110; δ_H (CD₃OD, 400 MHz) 2.27 (3H, s), 2.41 (3H, s), 2.61 (6H, s), 4.19 (2H, s), 6.76 (1H, d), 6.88-6.93 (2H, m), 7.20 (1H, d), 7.82 (1H, d), 8.03 (1H, d); MS m/z (TS⁺) 367 (MH⁺).

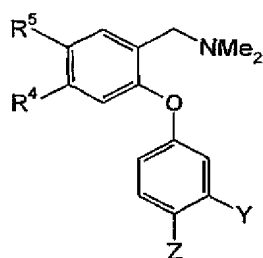
10 EXAMPLE 25**N-{5-Methoxy-2-[3-methyl-4-(methylsulfanyl)phenoxy]benzyl}-N,N-dimethylamine**

- Dimethylamine hydrochloride (424 mg, 5.2 mmol), Et₃N (725 μ L, 5.2 mmol), AcOH (298 μ L, 5.2 mmol) and sodium triacetoxyborohydride (1.10 g, 5.2 mmol) were added to a
- 15 solution of the aldehyde from Preparation 24 (1.00 g, 3.47 mmol) in THF (15 mL) and DCM (15 mL) and the mixture was stirred at room temperature for 16 h. After removing the solvent *in vacuo* the residue was taken up in 2M HCl (20 mL) and washed with ether (2 \times 15 mL). The aqueous layer was basified with NaOH pellets and extracted with DCM (4 \times 20 mL). The combined DCM extracts were washed with brine, dried (MgSO₄) and
- 20 evaporated. The residue was taken up in a small amount of DCM and treated with 1M

ethereal HCl to precipitate the HCl salt. This was filtered, washed with ether and dried to give a white solid (936 mg) contaminated with triethylamine hydrochloride. This was dissolved in 1M NaOH (10 mL) and extracted with EtOAc (3×15 mL). The organic extracts were washed with brine (10 mL), dried (MgSO₄) and evaporated before being re-dissolved in EtOAc and evaporated again. The residue was taken up in DCM and treated with 1M ethereal HCl to precipitate the HCl salt, which was filtered, washed with ether and dried to give a white solid (635 mg, 52%); δ_H (CDCl₃, 300 MHz) 2.35 (3H, s), 2.45 (3H, s), 2.79 (6H, s), 3.90 (3H, s), 4.21 (2H, s), 6.70 (1H, d), 6.73 (1H, s), 6.90 (2H, m), 7.18 (1H, d), 7.65 (1H, s), 12.83 (1H, brs); MS m/z (TS⁺) 318 (MH⁺).

10

Compounds of formula If, i.e. compounds of general formula I where R¹ and R² are methyl, shown in Table 3 were prepared according to Example 25 from the precursors indicated.

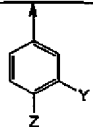
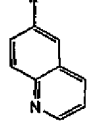
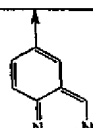
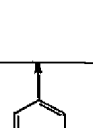
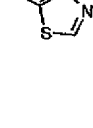
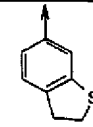


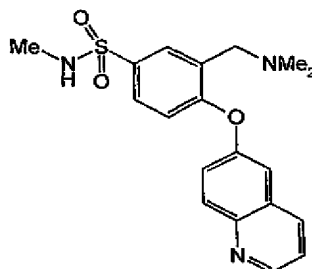
(If)

Table 3

15

Example	Precursor	R ⁴	R ⁵		data
26	Prep 25	H	F		HCl salt: δ_H (CDCl ₃ , 300 MHz) 2.23 (6H, s), 3.41 (2H, s), 6.98 (2H, m), 7.34 (2H, m), 7.48 (1H, dd), 7.98 (1H, d), 8.08 (1H, d), 8.80 (1H, s); MS m/z (TS ⁺) 297 (MH ⁺)
27	Prep 39	H	-NO ₂		δ_H (CDCl ₃ , 300 MHz) 2.32 (6H, s), 2.36 (3H, s), 2.47 (3H, s), 3.60 (2H, s), 6.80 (1H, d), 6.87 (2H, d), 7.19 (1H, d), 8.03 (1H, d), 8.40 (1H, d); MS m/z (ES ⁺) 333 (MH ⁺)
28	Prep 38	H	-NO ₂		Taken on crude at ~75% purity; δ_H (CDCl ₃ , 400 MHz) 2.33 (6H, s), 3.24 (2H, m), 3.38 (2H, m), 3.66 (2H, s), 6.76 (2H, m), 6.86 (1H, m), 7.17 (1H, d), 8.00 (1H, dd), 8.37 (1H, d)

Example	Precursor	R ⁴	R ⁵		data
29	Prep 26	H	H		δ_H (CDCl ₃ , 300 MHz) 2.28 (6H, s), 3.50 (2H, s), 7.03 (2H, m), 7.20-7.40 (3H, m), 7.52 (2H, m), 7.98 (1H, d), 8.09 (1H, d), 8.81 (1H, m); MS m/z (TS ⁺) 279 (MH ⁺)
30	Prep 27	H	H		HCl salt: δ_H (d ₆ -DMSO, 300 MHz) 2.77 (6H, d), 4.38 (2H, d), 7.08 (1H, d), 7.36 (1H, t), 7.52 (1H, t), 7.62 (1H, s), 7.80 (1H, d), 7.91 (1H, dd), 8.10 (1H, d), 9.25 (1H, s), 9.52 (1H, s); MS m/z (TS ⁺) 280 (MH ⁺)
31	Prep 29	H	H		Maleate salt: δ_H (d ₆ -DMSO, 300 MHz) 2.77 (6H, s), 4.33 (2H, s), 5.98 (2H, s), 6.87 (1H, d), 7.21 (1H, dt), 7.30 (1H, dd), 7.41 (1H, dt), 7.58 (1H, dd), 7.88 (1H, d), 8.11 (1H, d), 9.32 (1H, s); MS m/z 285 (MH ⁺)
32	Prep 33	H	Br		HCl salt: δ_H (DMSO-d ₆ , 400 MHz) 2.77 (6H, d), 3.23 (3H, m), 3.39 (2H, m), 4.32 (2H, d), 6.75 (2H, m), 7.03 (1H, s), 7.26 (1H, d), 7.57 (1H, dd), 7.87 (1H, s), 10.06 (1H, br, s); MS m/z (ES ⁺) 366 (MH ⁺)
33	Prep 32	Br	H		δ_H (CDCl ₃ , 400 MHz) 2.22 (6H, s), 2.30 (3H, s), 2.41 (3H, s), 3.41 (2H, s), 6.76 (2H, m), 6.94 (1H, s), 7.18 (1H, s), 7.21 (1H, obs), 7.30 (1H, d); MS m/z (TS ⁺) 366/368 (MH ⁺)

EXAMPLE 34**3-[(Dimethylamino)methyl]-N-methyl-4-(6-quinolinylloxy)benzenesulfonamide**

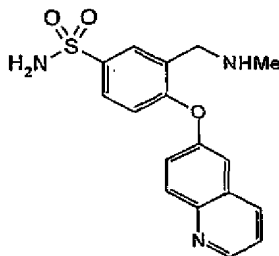
- 5 Chlorosulfonic acid (106 μ L, 1.6 mmol) was added to a solution of Example 29 (50 mg, 0.16 mmol) in DCM (2 mL) and the mixture was stirred for 3 h at room temperature. Water (2 mL) was added, the mixture was adjusted to pH 6 with sat aq NaHCO₃ and extracted with DCM (2 \times 5 mL). The organic extracts were dried (MgSO₄) and filtered and

8M methylamine in EtOH (0.3 mL) was added. After standing for 1 h the solvent was removed *in vacuo* and the residue was purified by column chromatography [SiO₂; 95:5:0.5 (DCM/ MeOH/ 880 NH₃)]. The product was taken up in EtOAc and converted to the HCl salt by the addition of ethereal HCl. This gave the desired product as a

5 hygroscopic solid (3 mg, 5%); δ_H (CD₃OD, 300 MHz) 2.60 (3H, s), 2.99 (6H, s), 4.60 (2H, s), 7.21 (1H, d), 7.96 (1H, d), 8.04 (3H, m), 8.19 (1H, s), 8.38 (1H, d), 9.03 (1H, d), 9.18 (1H, d); MS *m/z* (TS⁺) 371 (MH⁺).

EXAMPLE 35

10 3-[(Methylamino)methyl]-4-(6-quinolinylloxy)benzenesulfonamide

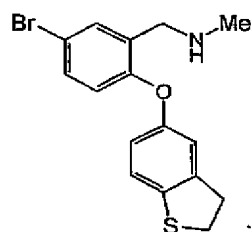


Trifluoroacetic anhydride (0.96 mL, 6.8 mmol) was added to a solution of the amine of Example 48 (900 mg, 3.4 mmol) and triethylamine (1.9 mL, 13.6 mmol) in CH₂Cl₂ (15 mL) at 0°C and the mixture was stirred for 5 min. The solvent was removed *in vacuo* and

15 the residue was partitioned between CH₂Cl₂ and water. The organic layer was washed with brine, dried (MgSO₄) and evaporated to give a yellow oil, which was used without further purification. This crude oil was taken up in CH₂Cl₂ (20 mL), cooled to 0°C and ClSO₃H (2.4 mL, 36.1 mmol) was added dropwise. The mixture was allowed to warm to room temperature and stirred for 4 h before being poured into ice water. The mixture

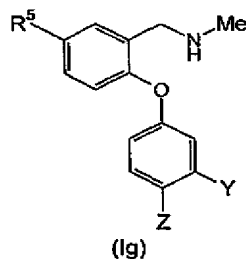
20 was extracted with CH₂Cl₂ (50 mL) and the organic layer was treated with a saturated solution of NH₃ in MeOH (10 mL). After stirring for 4 h 1M LiOH (20 mL) was added and stirring was continued overnight. Tlc analysis indicated reaction was incomplete so further 1M LiOH (50 mL) was added and the mixture was stirred for 2 h. The mixture was acidified to pH 8 with 2M HCl and extracted with CH₂Cl₂ (3×200 mL). The combined

25 organic extracts were dried (MgSO₄) and evaporated and the residue was triturated with ether to give the title compound (500 mg, 43%) as a yellow solid; δ_H (CDCl₃, 400 MHz) 2.46 (3H, s), 3.87 (2H, s), 6.93 (1H, d), 7.25 (1H, s), 7.39 (1H, t), 7.42 (1H, d), 7.78 (1H, d), 8.00-8.08 (2H, m), 8.12 (1H, d), 8.86 (1H, s); MS *m/z* (ES⁺) 344 (MH⁺).

EXAMPLE 36**N-[5-Bromo-2-(2,3-dihydro-1-benzothien-5-yloxy)benzyl]-N-methylamine**

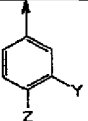
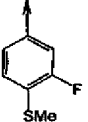
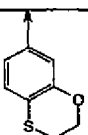
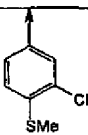
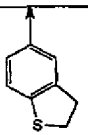
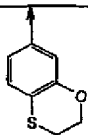
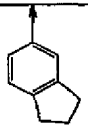
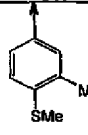
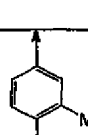
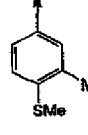
The aldehyde of Preparation 19 (1.10 g, 3.28 mmol) was dissolved in 8M methylamine in
 5 EtOH (4.1 mL, 32.8 mmol) and stirred for 5 h before the portionwise addition of NaBH₄
 (372 mg, 9.83 mmol) over 30 min. EtOH (100 mL) was added and the reaction was
 stirred for 16 h before being concentrated *in vacuo*. The residue was quenched with 6M
 HCl until pH 1 and the precipitated HCl salt was collected by filtration, washed with water
 (100 mL) and dried *in vacuo* to give a crystalline solid (1.04 g, 82%); δ_H (CDCl₃, 400
 10 MHz) 2.62 (3H, s), 3.26 (2H, t), 3.41 (2H, t), 4.18 (2H, s), 6.66 (1H, d), 6.90 (1H, d), 7.03
 (1H, s), 7.19 (1H, d), 7.39 (1H, d), 7.80 (1H, s); MS *m/z* (ES⁺) 350, 352 (MH⁺).

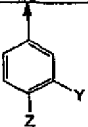

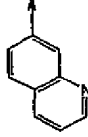
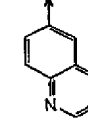
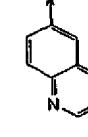
Compounds of formula Ig, i.e. compounds of general formula I where R¹ and R⁴ are
 hydrogen and R² is methyl, shown in Table 4 were prepared according to Example 36
 15 from the precursors indicated. For those compounds which were isolated as the free
 base the reaction mixture was partitioned between 2M HCl and ether after removal of
 the reaction solvent *in vacuo*. The aqueous layer was then basified and extracted with
 DCM, the DCM layer being dried (MgSO₄) and evaporated to give the desired secondary
 amine.



20

Table 4

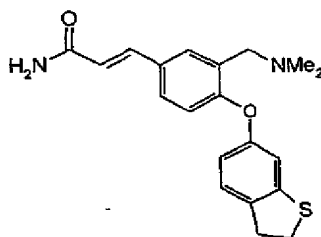
Example	Precursor	R ⁵		data
37	Prep 20	Br		HCl salt: δ_H (d_6 -DMSO, 300 MHz) 2.48 (3H, s), 2.59 (3H, s), 4.18 (2H, s), 6.88 (1H, d), 7.01 (1H, d), 7.16 (1H, d), 7.45 (1H, t), 7.59 (1H, d), 7.91 (1H, s); MS m/z (TS ⁺) 356, 358 (MH ⁺)
38	Prep 21	Br		δ_H (CDCl ₃ , 400 MHz) 2.43 (3H, s), 3.11 (2H, t), 3.78 (2H, s), 4.41 (2H, t), 6.44 (1H, s), 6.51 (1H, d), 6.77 (1H, d), 6.98 (1H, d), 7.31 (1H, d), 7.55 (1H, s); MS m/z (ES ⁺) 366, 368 (MH ⁺)
39	Prep 22	Br		δ_H (CDCl ₃ , 400 MHz) 2.41 (3H, s), 2.45 (3H, s), 3.72 (2H, s), 6.77 (1H, d), 6.85 (1H, d), 6.99 (1H, s), 7.18 (1H, d), 7.36 (1H, d), 7.59 (1H, s); MS m/z (TS ⁺) 372, 374 (MH ⁺)
40	Prep 38	-NO ₂		δ_H (CDCl ₃ , 300 MHz) 2.55 (3H, s), 3.30 (2H, m), 3.43 (2H, m), 3.95 (2H, s), 6.80 (2H, m), 6.91 (1H, s), 7.22 (1H, d), 8.05 (1H, d), 8.40 (1H, s); MS m/z (ES ⁺) 317 (MH ⁺)
41	Prep 36	-NO ₂		δ_H (CDCl ₃ , 400 MHz) 2.45 (3H, s), 3.10 (2H, m), 3.86 (2H, s), 4.40 (2H, m), 6.53 (2H, m), 6.80 (1H, d), 7.01 (1H, d), 8.00 (1H, d), 8.27 (1H, s); MS m/z (TS ⁺) 333 (MH ⁺)
42	Prep 40	-NO ₂		δ_H (CDCl ₃ , 400 MHz) 2.14 (2H, m), 2.52 (3H, s), 2.93 (4H, t), 3.92 (2H, s), 6.78 (1H, d), 6.81 (1H, d), 6.91 (1H, s), 7.22 (1H, d), 8.02 (1H, dd), 8.29 (1H, s); MS m/z (TS ⁺) 299 (MH ⁺)
43	Prep 24	-OMe		HCl salt: δ_H (CDCl ₃ , 300 MHz) 2.35 (3H, s), 2.45 (3H, s), 2.60 (3H, s), 3.84 (3H, s), 4.17 (2H, s), 6.80 (1H, d), 6.82 (1H, s), 6.88 (2H, s), 7.15 (1H, d), 7.42 (1H, s), 9.85 (2H, brs); MS m/z (TS ⁺) 304 (MH ⁺)
44	Prep 23	Br		δ_H (CDCl ₃ , 300 MHz) 2.35 (3H, s), 2.45 (6H, s), 3.77 (2H, s), 6.73 (2H, m), 6.80 (1H, s), 7.19 (1H, d), 7.32 (1H, d), 7.57 (1H, s); MS m/z (TS ⁺) 352, 354 (MH ⁺)
45	Prep 30	H		HCl salt: δ_H (d_6 -DMSO, 400 MHz) 2.22 (3H, s), 2.42 (3H, s), 2.58 (3H, s), 4.18 (2H, s), 6.78 (1H, d), 6.96 (1H, d), 6.99 (1H, s), 7.18 (1H, t), 7.25 (1H, d), 7.38 (1H, t), 7.60 (1H, d); MS m/z (ES ⁺) 274 (MH ⁺)

Example	Precursor	R ⁵		data
46	Prep 31	H		HCl salt: δ_H (CDCl ₃ , 400 MHz) 2.55 (3H, brs), 3.21 (2H, t), 3.32 (2H, m), 4.17 (2H, s), 6.76 (1H, d), 6.84 (1H, d), 6.99 (1H, s), 7.04 (1H, m), 7.12 (1H, d), 7.28 (1H, obs), 7.61 (1H, d); MS m/z (ES ⁺) 272 (MH ⁺)
47	Prep 28	H		Maleate salt: δ_H (DMSO-d ₆ , 400 MHz) 2.60 (3H, s), 4.19 (2H, s), 5.99 (2H, s), 7.03 (1H, d), 7.29 (1H, m), 7.37 (1H, s), 7.45 (3H, m), 7.60 (1H, d), 8.06 (1H, d), 8.37 (1H, d), 8.74 (2H, br), 8.83 (1H, dd); MS m/z 264 (MH ⁺)
48	Prep 26	H		δ_H (CDCl ₃ , 300 MHz) 2.64 (3H, s), 4.25 (2H, s), 6.89 (1H, d), 7.19 (1H, t), 7.30-7.41 (2H, m), 7.45 (1H, s), 7.49 (1H, d), 7.69 (1H, d), 8.08 (1H, d), 8.16 (1H, d), 8.87 (1H, d); MS m/z (ES ⁺) 529 (2M+H ⁺)
49	Prep 34	-CN		HCl salt: δ_H (CD ₃ OD, 400 MHz) 2.81 (3H, s), 3.30 (1H, br), 4.42 (2H, s), 7.17 (1H, br), 7.82 (1H, br), 8.06 (1H, br), 8.11 (3H, br), 8.39 (1H, br), 9.18 (1H, br), 9.21 (1H, br); MS m/z (ES ⁺) 290 (MH ⁺)

^a – 2M Methylamine in MeOH (2 equiv.) and Ti(OⁱPr)₄ (2 equiv.) in EtOH (~0.1 M soln of aldehyde) were used in place of methylamine in EtOH. After isolation of the free base it was converted to the maleate salt by standard methods.

5 EXAMPLE 50

(2E)-3-{4-(2,3-Dihydro-1-benzothien-6-yloxy)-3-[(dimethylamino)methyl]phenyl}-2-propenamide

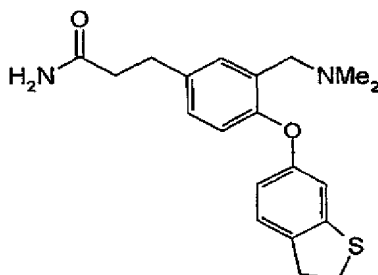


- 10 A mixture of the bromide of Example 32 (400 mg, 1.10 mmol), acrylamide (156 mg, 2.19 mmol), triethylamine (0.38 mL, 2.74 mmol), palladium II acetate (12.5 mg, 0.06 mmol) and tri-*o*-tolylphosphine (33.4 mg, 0.11 mmol) in acetonitrile (15 mL) was heated at reflux for 72 h. After cooling to room temperature the solvent was removed *in vacuo* and

the residue was partitioned between EtOAc (50 mL) and 2M HCl (50 mL). The aqueous phase was basified with 2M NaOH and extracted with EtOAc (3×50 mL). The combined basic extracts were dried (MgSO₄) and evaporated. The residue was purified by column chromatography [SiO₂; 96:4:0.5 (DCM/ MeOH/ 880 NH₃) increasing polarity to 90:10:1] to give the title compound (196 mg, 50%) as a beige foam; δ_H (CDCl₃, 400 MHz) 2.28 (6H, s), 3.24 (2H, t), 3.38 (2H, t), 3.51 (2H, s), 5.73 (2H, br), 6.42 (1H, d), 6.59 (1H, dd), 6.82 (2H, m), 7.10 (1H, d), 7.32 (1H, d), 7.60 (1H, d), 7.69 (1H, s); MS *m/z* (ES⁺) 355 (MH⁺).

10 EXAMPLE 51

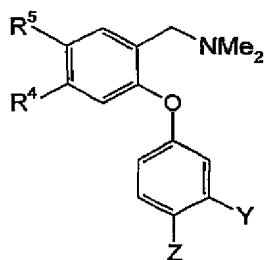
3-{4-(2,3-Dihydro-1-benzothien-6-yloxy)-3-[(dimethylamino)methyl]phenyl}propanamide



A solution of SmI₂ in THF (0.1 M, 21.9 mL, 2.19 mmol) was added to a solution of the alkene of Example 50 (194 mg, 0.55 mmol) in THF (5 mL) under nitrogen followed by water (1 mL). After stirring at room temperature for 10 min the reaction was quenched with 6M NaOH (10 mL) and stirred for 30 min. The organic phase was separated and the aqueous phase was extracted with EtOAc (2×20 mL). The combined organic layers were dried (MgSO₄) and evaporated to an oil, which was purified by column chromatography [SiO₂; 93:7:1 (DCM/ MeOH/ 880 NH₃) increasing polarity to 90:10:1] to give the title compound (90 mg, 46%); δ_H (CDCl₃, 400 MHz) 2.25 (6H, s), 2.54 (2H, t), 2.97 (2H, t), 3.22 (2H, t), 3.36 (2H, t), 3.42 (2H, s), 5.20-5.46 (2H, br), 6.54 (1H, d), 6.73 (1H, s), 6.81 (1H, d), 7.05 (2H, m), 7.31 (1H, s); MS *m/z* (TS⁺) 357 (MH⁺).

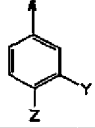
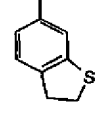
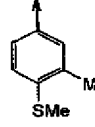
Compounds of formula If, i.e. compounds of general formula I where R¹ and R² are methyl, shown in Table 5 were prepared according to Preparation 50 from the precursors indicated.

45



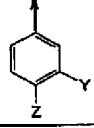
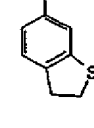
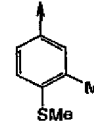
(If)

Table 5

Example	Precursor	R ⁴	R ⁵		data
52	Example 32	H	-CO ₂ Me		δ_H (CDCl ₃ , 400 MHz) 2.29 (6H, s), 3.26 (3H, m), 3.39 (2H, m), 3.54 (2H, s), 3.89 (3H, s), 6.62 (1H, d), 6.84 (2H, m), 7.13 (1H, d), 7.86 (1H, d), 8.12 (1H, s); MS <i>m/z</i> (TS ⁺) 344 (MH ⁺)
53	Example 33	-CO ₂ Me	H		δ_H (CDCl ₃ , 400 MHz) 2.24 (6H, s), 2.33 (3H, s), 2.42 (3H, s), 3.48 (2H, s), 3.82 (3H, s), 6.73 (2H, m), 7.14 (1H, d), 7.50 (1H, s), 7.55 (1H, d), 7.78 (1H, d); MS <i>m/z</i> (TS ⁺) 346 (MH ⁺)

- 5 Compounds of formula If, i.e. compounds of general formula I where R¹ and R² are methyl, shown in Table 6 were prepared according to Preparation 55 from the precursors indicated.

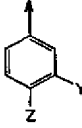
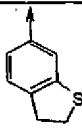
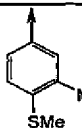
Table 6

Example	Precursor	R ⁴	R ⁵		data
54	Example 52	H	-CO ₂ H		δ_H (CD ₃ OD, 400 MHz) 2.95 (6H, s), 3.29 (2H, m), 3.42 (2H, m), 4.52 (2H, s), 6.80 (1H, d), 6.89 (1H, d), 7.03 (1H, s), 7.29 (1H, d), 8.06 (1H, d), 8.23 (1H, s); MS <i>m/z</i> (TS ⁺) 330 (MH ⁺)
55 (~80% purity)	Example 55	-CO ₂ H	H		δ_H (CD ₃ OD, 400 MHz) 2.27 (3H, s), 2.42 (3H, s), 2.88 (6H, s), 4.43 (2H, s), 6.95 (2H, m), 7.26 (1H, m), 7.42 (2H, m), 7.72 (1H, m)

Compounds of formula If, i.e. compounds of general formula I where R¹ and R² are methyl, shown in Table 7 were prepared according to Preparation 59 from the precursors indicated.

5

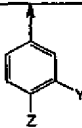
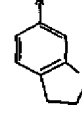
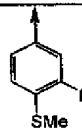
Table 7

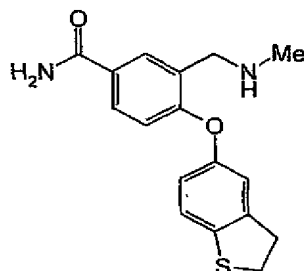
Example	Precursor	R ⁴	R ⁵		data
56	Example 54	H	-CONH ₂		δ_H (CDCl ₃ , 400 MHz) 2.27 (6H, s), 3.25 (2H, m), 3.38 (2H, m), 3.54 (2H, s), 5.90-6.38 (2H, br), 6.59 (1H, d), 6.80 (1H, s), 6.86 (1H, d), 7.11 (1H, d), 7.71 (1H, d), 7.92 (1H, s); MS <i>m/z</i> (TS ⁺) 329 (MH ⁺)
57	Example 55	-CONH ₂	H		HCl salt: δ_H (CD ₃ OD, 400 MHz) 2.32 (3H, s), 2.43 (3H, s), 2.94 (6H, s), 4.47 (2H, s), 6.98 (2H, br), 7.27 (1H, br), 7.36 (1H, br), 7.62 (1H, br); MS <i>m/z</i> (TS ⁺) 331 (MH ⁺)

Compounds of formula If, i.e. compounds of general formula I where R¹ and R² are methyl, shown in Table 8 were prepared according to Preparation 69 from the precursors indicated

10

Table 8

Example	Precursor	R ⁴	R ⁵		data
58	Example 52	H	-CH ₂ OH		HCl salt: δ_H (DMSO-d ₆ , 400 MHz) 2.76 (6H, s), 3.22 (2H, m), 3.40 (2H, m), 4.30 (2H, s), 4.49 (2H, s), 5.27 (1H, br, s), 6.68 (1H, d), 6.83 (1H, d), 6.97 (1H, s), 7.25 (1H, d), 7.37 (1H, d), 7.60 (1H, s), 10.07 (1H, br); MS <i>m/z</i> (TS ⁺) 316 (MH ⁺)
59	Example 53	-CH ₂ OH	H		HCl salt: δ_H (CD ₃ OD, 400 MHz) 2.34 (3H, s), 2.46 (3H, s), 2.90 (6H, s), 4.40 (2H, s), 4.55 (2H, s), 6.89 (1H, s), 6.95 (2H, m), 7.18 (1H, d), 7.28 (1H, d), 7.50 (1H, d); MS <i>m/z</i> (TS ⁺) 318 (MH ⁺)

EXAMPLE 60**4-(2,3-Dihydro-1-benzothien-5-yloxy)-3-[(methylamino)methyl]benzamide**

- The protected amine of Preparation 59 (317 mg, 0.76 mmol) was dissolved in a saturated solution of HCl in DCM (25 mL) at 0°C and left for 1 h before being neutralised by the addition of 10% aq K₂CO₃ (25 mL). Water (50 mL) was added and the layers were separated. The aqueous layer was extracted with DCM (25 mL) and the combined organic layers were dried (MgSO₄) and evaporated. The resulting oil was dissolved in EtOAc (10 mL) and treated with 1M ethereal HCl (1 mL). The white precipitate was collected by filtration and dried *in vacuo* to give the desired product (211 mg, 77%); δ_H (CD₃OD, 400 MHz) 2.77 (3H, s), 3.35 (2H, obs), 3.39 (2H, t), 4.34 (2H, s), 6.79 (1H, d), 6.90 (1H, dd), 7.02 (1H, s), 7.21 (1H, d), 7.83 (1H, d), 8.00 (1H, s); MS *m/z* (TS⁺) 315 (MH⁺).
- Compounds of formula Ig, i.e. compounds of general formula I where R¹ and R⁴ are hydrogen and R² is methyl, shown in Table 9 were prepared according to Example 60 from the precursors indicated.

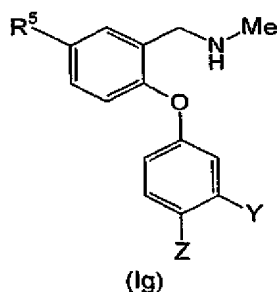
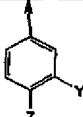
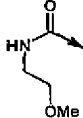
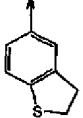
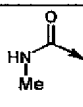
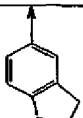
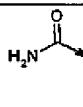
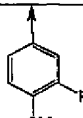
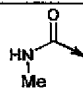
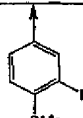
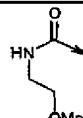
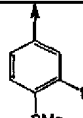
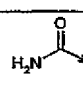
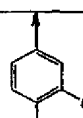
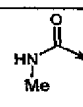
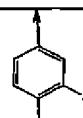
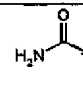
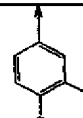
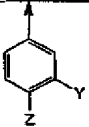
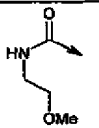
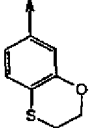

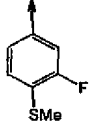

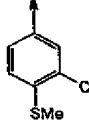
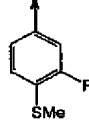

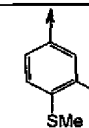

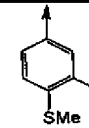

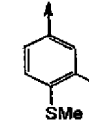

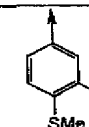


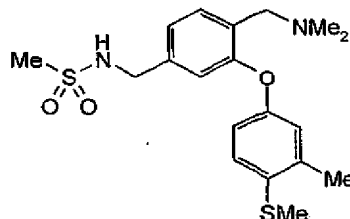
Table 9

Ex	Prec	R ⁵		data
61	Prep 61			HCl salt: δ_H (CDCl ₃ , 400 MHz) 2.77 (3H, d), 3.35 (2H, obs), 3.36 (3H, s), 3.39 (2H, t), 3.51 (4H, s), 4.35 (2H, s), 6.80 (1H, d), 6.90 (1H, dd), 7.01 (1H, s), 7.21 (1H, d), 7.79 (1H, d), 7.96 (1H, s); MS <i>m/z</i> (TS ⁺) 373 (MH ⁺)
62	Prep 60			HCl salt: δ_H (CD ₃ OD, 400 MHz) 2.77 (3H, s), 2.88 (3H, s), 3.35 (2H, obs), 3.39 (2H, t), 4.35 (2H, s), 6.79 (1H, d), 6.90 (1H, dd), 7.01 (1H, s), 7.20 (1H, d), 7.78 (1H, d), 7.96 (1H, s); MS <i>m/z</i> (TS ⁺) 329 (MH ⁺)
63	Prep 62			HCl salt: δ_H (d ₆ -DMSO, 300 MHz) 2.52 (3H, obs), 2.61 (3H, s), 4.21 (3H, s), 6.90 (1H, d), 7.07 (1H, d), 7.19 (1H, d), 7.40 (1H, brs), 7.48 (1H, t), 7.92 (1H, d), 7.96 (1H, s), 8.21 (1H, s); MS <i>m/z</i> (TS ⁺) 321 (MNH ₄ ⁺)
64	Prep 63			HCl salt: δ_H (d ₆ -DMSO, 300 MHz) 2.52 (3H, obs), 2.60 (3H, s), 2.79 (3H, d), 4.21 (2H, s), 6.89 (1H, d), 7.07 (1H, d), 7.19 (1H, d), 7.48 (1H, t), 7.85 (1H, d), 8.19 (1H, s), 8.48 (1H, d); MS <i>m/z</i> (TS ⁺) 335 (MH ⁺)
65	Prep 64			HCl salt: δ_H (d ₆ -DMSO, 300 MHz) 2.52 (3H, obs), 2.60 (3H, s), 3.27 (3H, s), 3.46 (4H, m), 4.22 (2H, s), 6.91 (1H, d), 7.08 (1H, d), 7.20 (1H, d), 7.50 (1H, t), 7.89 (1H, d), 8.10 (1H, s), 8.58 (1H, brs); MS <i>m/z</i> (TS ⁺) 379 (MH ⁺)
66	Prep 65			HCl salt: δ_H (d ₆ -DMSO, 300 MHz) 2.52 (3H, obs), 2.60 (3H, t), 4.11 (2H, s+H ₂ O), 6.82 (1H, d), 7.21 (1H, d), 7.40 (3H, s+d), 7.88 (1H, d), 7.96 (1H, brs), 8.21 (1H, s); MS <i>m/z</i> (ES ⁺) 337 (MH ⁺)
67	Prep 66			HCl salt: δ_H (d ₆ -DMSO, 300 MHz) 2.52 (3H, obs), 2.60 (3H, t), 2.79 (3H, d), 4.22 (2H, t), 6.94 (1H, d), 7.22 (1H, d), 7.40 (2H, s+d), 7.83 (1H, d), 8.19 (1H, d), 8.46 (1H, d); MS <i>m/z</i> (ES ⁺) 351 (MH ⁺)
68	Prep 67			δ_H (CDCl ₃ , 400 MHz) 2.41 (3H, s), 3.08 (2H, m), 3.80 (2H, s), 4.37 (2H, m), 5.94-6.36 (2H, brd), 6.46 (1H, s), 6.49 (1H, d), 6.81 (1H, d), 6.96 (1H, d), 7.65 (1H, d), 7.86 (1H, s); MS <i>m/z</i> (TS ⁺) 331 (MH ⁺)

Ex	Prec	R ⁵		data
69	Prep 68			HCl salt: δ_H (CDCl ₃ , 400 MHz) 2.42 (3H, s), 3.08 (2H, m), 3.44-3.50 (4H, m), 3.80 (2H, s), 4.40 (2H, m), 6.45 (1H, s), 6.49 (1H, d), 6.62 (1H, brs), 6.83 (1H, d), 6.96 (1H, d), 7.62 (1H, d), 7.78 (1H, s); MS m/z (TS ⁺) 390 (MH ⁺)
70	Prep 70			HCl salt: δ_H (d ₆ -DMSO, 300 MHz) 2.48 (3H, s), 2.58 (3H, s), 4.12 (2H, s), 4.50 (2H, d), 5.32 (1H, t), 6.92 (2H, m), 7.03 (1H, dd), 7.39 (1H, dd), 7.46 (1H, d), 7.60 (1H, s); MS m/z (TS ⁺) 308 (MH ⁺)
71	Prep 69			HCl salt: δ_H (d ₆ -DMSO, 300 MHz) 2.52 (3H, obs), 2.58 (3H, t), 4.10 (2H, s+H ₂ O), 4.48 (2H, s), 6.94 (1H, d), 7.11 (1H, d), 7.21 (1H, s), 7.25 (2H, m), 7.57 (1H, s); MS m/z (ES ⁺) 324 (MH ⁺)
72	Prep 49	-C≡N		HCl salt: δ_H (d ₆ -DMSO, 300 MHz) 2.52 (3H, s), 2.60 (3H, s), 4.24 (2H, s), 6.94 (1H, d), 7.04 (1H, d), 7.28 (1H, d), 7.50 (1H, t), 7.86 (1H, d), 8.08 (1H, s); MS m/z (TS ⁺) 303 (MH ⁺)
73	Prep 73			HCl salt: δ_H (CDCl ₃ , 300 MHz) 2.48 (3H, s), 2.64 (3H, s), 2.99 (3H, s), 4.23 (2H, s), 4.30 (2H, d), 6.40 (1H, br), 6.81-6.89 (3H, m), 7.26-7.35 (2H, obs), 7.92 (1H, s); MS m/z (ES ⁺) 385 (MH ⁺), (ES ⁻) 383 (M-H ⁺)
74	Prep 71			HCl salt: δ_H (CD ₃ OD, 400 MHz) 2.30 (3H, s), 2.44 (3H, s), 2.73 (3H, s), 4.25 (2H, s), 4.59 (2H, s), 6.81 (1H, d), 6.88-6.92 (2H, m), 7.24 (1H, d), 7.37 (1H, d), 7.46 (1H, s); MS m/z (ES ⁺) 304 (MH ⁺)
75	Prep 72			HCl salt: δ_H (CD ₃ OD, 300 MHz) 2.37 (3H, s), 2.48 (3H, s), 2.78 (3H, s), 2.96 (3H, s), 4.27 (2H, s), 4.31 (2H, s), 6.85 (1H, d), 6.92-7.00 (2H, m), 8.31 (1H, d), 7.41 (1H, d), 7.57 (1H, s); MS m/z (ES ⁺) 381 (MH ⁺), (ES ⁻) 379 (M-H ⁺)
76	Prep 75			HCl salt: δ_H (CD ₃ OD, 400 MHz) 2.29 (3H, s), 2.41 (3H, s), 2.43 (3H, s), 3.76 (2H, s), 4.30 (2H, s), 6.72-6.79 (3H, m), 7.12 (1H, br), 7.27 (2H, obs); MS m/z (ES ⁺) 435 (MH ⁺), (ES ⁻) 433 (M-H ⁺)

EXAMPLE 77

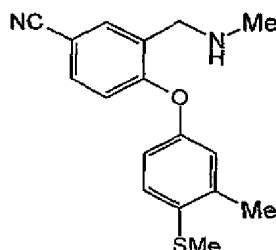
N-[4-[(Dimethylamino)methyl]-3-[3-methyl-4-(methylsulfanyl)phenoxy]benzyl]methanesulfonamide



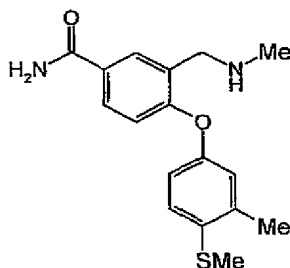
- 5 Example 77 was prepared from the Boc protected sulfonamide of Preparation 74 by the method of Example 60 ;HCl salt: δ_H (CD_3OD , 400 MHz) 2.29 (3H, s), 2.42 (3H, s), 2.82 (3H, s), 2.89 (6H, s), 4.17 (2H, s), 4.39 (2H, s), 6.39 (3H, m), 7.19 (1H, d), 7.24 (1H, d), 7.48 (1H, d); MS m/z (TS^+) 395 (MH^+).

EXAMPLE 78

3-[(Methylamino)methyl]-4-[3-methyl-4-(methylsulfanyl)phenoxy]benzonitrile

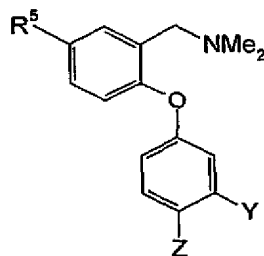


- Zn(CN)₂ (700 mg, 5.96 mmol) and Pd(PPh₃)₄ (1.97 g, 1.7 mmol) were added to a solution of the bromide of Example 44 (3.0 g, 8.52 mmol) in DMF (20 mL) and the mixture was heated at 100°C for 17 h. The reaction was cooled to room temperature, diluted with water (100 mL) and extracted with ether (2×100 mL then 3×50 mL). The combined organic layers were washed with water (3×50 mL), dried (MgSO₄) and evaporated to a yellow oil. Initial purification by column chromatography [SiO₂; 95:5:0.5 (DCM/ MeOH/ 880 NH₃)] was unsuccessful so the material was re-chromatographed [SiO₂; 50% pentane in 95:5:0.5 (DCM/ MeOH/ 880 NH₃) increasing polarity to 0% pentane] to give the product (1.275 g, 50%) as a pale yellow oil. A sample was taken up in DCM (5 mL) and treated with 1M ethereal HCl to give the HCl salt as a white powder which was collected by filtration; δ_H ($CDCl_3$, 300 MHz) 2.35 (3H, s), 2.47 (6H, s), 3.88 (2H, s), 6.79 (1H, d), 6.87 (2H, m), 7.20 (1H, d), 7.46 (1H, d), 7.72 (1H, s); MS m/z (TS^+) 299 (MH^+).

EXAMPLE 79**3-[(Methylamino)methyl]-4-[3-methyl-4-(methylsulfanyl)phenoxy]benzamide**

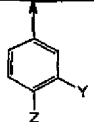

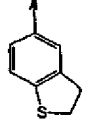
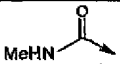
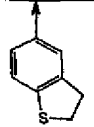
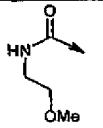
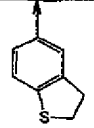

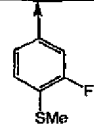

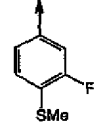
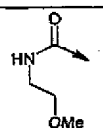
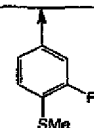

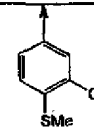

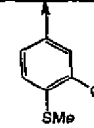
A mixture of the nitrile of Example 78 (404 mg, 1.35 mmol) and KOH (304 mg, 5.42 mmol) in *tert*-butanol (10 mL) was heated at reflux for 1 h under N₂. After cooling to room temperature the solvent was removed *in vacuo* and the residue was partitioned between water (10 mL) and DCM (10 mL). The aqueous layer was extracted with DCM (4 × 20 mL) and the combined organic layers were washed with brine, dried (MgSO₄) and evaporated. The residue was purified by column chromatography [SiO₂; 93:7:1 (DCM/ MeOH/ 880 NH₃)] to give the desired product (376 mg, 88%) as a white foam; δ_H (CDCl₃, 300 MHz) 2.35 (3H, s), 2.47 (3H, s), 2.49 (3H, s), 3.88 (2H, s), 5.90-6.30 (2H, brs), 6.82 (3H, m), 7.19 (1H, d), 7.70 (1H, d), 7.90 (1H, s); MS *m/z* (TS⁺) 317 (MH⁺).

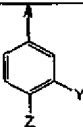

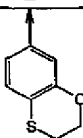
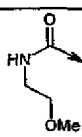
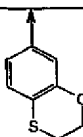

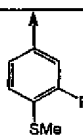

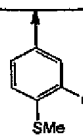
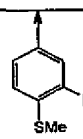
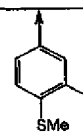
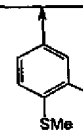
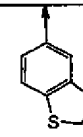
Compounds of formula 1h, i.e. compounds of general formula I where R¹ and R² are methyl and R⁴ is hydrogen, shown in Table 10 where prepared according to Example 12 from the precursors indicated.

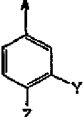
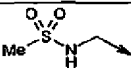

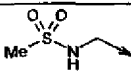
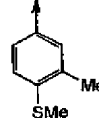

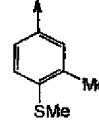
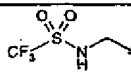
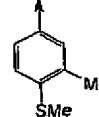

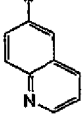


(1h)

Table 10

Example	Precursor	R ⁵		data
80	Example 60			δ_H (CD ₃ OD, 400 MHz) 2.91 (6H, s), 3.35 (2H, obs), 3.38 (2H, t), 4.45 (2H, s), 6.81 (1H, d), 6.90 (1H, d), 7.03 (1H, s), 7.21 (1H, d), 7.86 (1H, d), 8.03 (1H, s); MS <i>m/z</i> (TS ⁺) 329 (MH ⁺)
81	Example 62			δ_H (CD ₃ OD, 400 MHz) 2.90-2.99 (9H, m), 3.35 (2H, obs), 3.43 (2H, t), 4.50 (2H, s), 6.88 (1H, d), 6.97 (1H, d), 7.07 (1H, s), 7.28 (1H, d), 7.85 (1H, d), 8.03 (1H, s); MS <i>m/z</i> (TS ⁺) 343 (MH ⁺)
82	Example 61			δ_H (CDCl ₃ , 400 MHz) 2.90 (6H, brm), 3.35 (2H, obs), 3.37 (2H, brm), 3.51 (4H, brm), 4.43 (2H, brs), 6.80-6.94 (2H, brd), 7.01 (1H, brs), 7.20 (1H, brs), 7.82 (1H, brs), 7.98 (1H, brs); MS <i>m/z</i> (TS ⁺) 387 (MH ⁺)
83	Example 63			δ_H (CDCl ₃ , 300 MHz) 2.29 (6H, s), 2.47 (3H, s), 3.51 (2H, s), 6.73 (2H, s), 6.97 (1H, d), 7.30 (1H, t), 7.79 (1H, d), 7.97 (1H, s); MS <i>m/z</i> (TS ⁺) 335 (MNH ₄ ⁺)
84	Example 64			δ_H (CDCl ₃ , 300 MHz) 2.29 (6H, s), 2.46 (3H, s), 3.02 (3H, d), 3.54 (2H, s), 6.20 (1H, brs), 6.69 (2H, m), 6.97 (1H, d), 7.30 (1H, t), 7.75 (1H, d), 7.91 (1H, s); MS <i>m/z</i> (TS ⁺) 349 (MH ⁺)
85	Example 65			HCl salt: δ_H (CDCl ₃ , 300 MHz) 2.49 (3H, s), 2.94 (6H, s), 3.42 (3H, s), 3.65 (4H, m), 4.33 (2H, s), 6.79 (2H, d), 6.96 (1H, d), 7.35 (1H, t), 7.39 (1H, brs), 7.98 (1H, d), 8.68 (1H, s); MS <i>m/z</i> (TS ⁺) 393 (MH ⁺)
86	Example 66			δ_H (CDCl ₃ , 400 MHz) 2.38 (6H, s), 2.47 (3H, s), 3.53 (2H, s), 6.88 (2H, d), 7.03 (1H, s), 7.19 (1H, d), 7.77 (1H, d), 7.95 (1H, s); MS <i>m/z</i> (ES ⁺) 351 (MH ⁺)
87	Example 67			δ_H (CDCl ₃ , 400 MHz) 2.27 (6H, s), 2.46 (3H, s), 3.01 (3H, d), 3.50 (2H, s), 6.19 (1H, brs), 6.88 (2H, m), 7.00 (1H, s), 7.19 (1H, d), 7.72 (1H, d), 7.85 (1H, s); MS <i>m/z</i> (ES ⁺) 365 (MH ⁺)

Example	Precursor	R ⁵		data
88	Example 68			HCl salt: δ_H (CDCl ₃ , 400 MHz) 2.25 (6H, s), 3.07 (2H, s), 3.49 (2H, s), 4.37 (2H, m), 5.47-6.22 (2H, brd), 6.44 (1H, s), 6.49 (1H, d), 6.86 (1H, d), 6.95 (1H, d), 7.68 (1H, d), 7.87 (1H, s); MS <i>m/z</i> (TS ⁺) 346 (MH ⁺)
89	Example 69			HCl salt: δ_H (CD ₃ OD, 400 MHz) 2.91 (6H, s), 3.13 (2H, s), 3.27 (3H, s), 4.39 (2H, s), 4.46 (2H, s), 6.64 (2H, s+d), 6.87 (1H, d), 7.08 (1H, d), 7.95 (1H, d), 8.00 (1H, s); MS <i>m/z</i> (TS ⁺) 403 (MH ⁺)
90	Example 70			HCl salt: δ_H (d ₆ -DMSO, 300 MHz) 2.46 (3H, s), 2.74 (6H, s), 4.29 (2H, s), 4.51 (2H, s), 5.32 (1H, brs), 6.93 (2H, d), 7.08 (1H, d), 7.41 (2H, m), 7.63 (1H, s); MS <i>m/z</i> (TS ⁺) 322 (MH ⁺)
91	Example 71			HCl salt: δ_H (d ₆ -DMSO, 400 MHz) 2.52 (3H, obs), 2.76 (6H, s), 4.09 (2H, s), 4.49 (2H, s), 5.32 (1H, brs), 6.87 (1H, d), 7.08 (1H, d), 7.26 (1H, s), 7.38 (2H, m), 7.60 (1H, s); MS <i>m/z</i> (ES ⁺) 338 (MH ⁺)
92	Example 78	-C≡N		HCl salt: δ_H (CDCl ₃ , 400 MHz) 2.35 (3H, s), 2.48 (3H, s), 2.87 (6H, d), 4.39 (2H, d), 6.85 (1H, d), 6.90 (1H, d), 6.93 (1H, dd), 7.21 (1H, d), 7.60 (1H, d), 8.17 (1H, s); MS <i>m/z</i> (TS ⁺) 313 (MH ⁺)
93	Example 72	-C≡N		HCl salt: δ_H (d ₆ -DMSO, 300 MHz) 2.49 (3H, obs), 2.79 (6H, s), 4.41 (2H, s), 6.97 (1H, d), 7.14 (1H, d), 7.32 (1H, d), 7.49 (1H, t), 7.87 (1H, d), 8.22 (1H, s); MS <i>m/z</i> (TS ⁺) 317 (MH ⁺)
94	Example 45	H		HCl salt: δ_H (d ₆ -DMSO, 400 MHz) 2.23 (3H, s), 2.42 (3H, s), 2.76 (6H, s), 4.34 (2H, s), 6.80 (1H, d), 7.97 (1H, dd), 7.00 (1H, s), 7.19 (1H, t), 7.24 (1H, d), 7.40 (1H, t), 7.67 (1H, d); MS <i>m/z</i> (ES ⁺) 288 (MH ⁺)
95	Example 46	H		HCl salt: δ_H (CDCl ₃ , 400 MHz) 2.74 (6H, s), 3.22 (2H, m), 3.38 (2H, m), 4.26 (2H, s), 6.71 (1H, d), 6.80 (2H, brm), 7.15 (2H, brm), 7.32 (1H, d), 7.79 (2H, d); MS <i>m/z</i> (ES ⁺) 286 (MH ⁺)

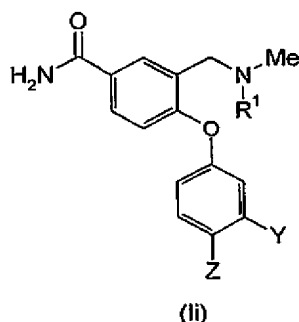
Example	Precursor	R ⁵		data
96	Example 73			HCl salt: δ_H (CD ₃ OD, 300 MHz) 2.46 (3H, s), 3.93 (6H, s), 3.97 (3H, s), 4.24 (2H, s), 4.42 (2H, s), 6.91-7.00 (3H, m), 7.41-7.54 (2H, m), 7.61 (1H, s); MS m/z (TS ⁺) 399 (MH ⁺), (ES ⁻) 397 (M-H ⁺)
97	Example 75			HCl salt: δ_H (CD ₃ OD, 400 MHz) 2.31 (3H, s), 2.43 (3H, s), 2.86-2.94 (9H, m), 4.22 (2H, s), 4.39 (2H, s), 6.83 (1H, d) 6.89-6.94 (2H, m), 7.26 (1H, d), 7.40 (1H, d), 7.54 (1H, s); MS m/z (ES ⁻) 393 (M-H ⁺)
98	Example 74			HCl salt: δ_H (CD ₃ OD, 300 MHz) 2.36 (3H, s), 2.47 (3H, s), 2.98 (6H, s), 4.43 (2H, s), 4.63 (2H, s), 6.89 (1H, d), 6.91-7.00 (2H, m), 7.30 (1H, d), 7.43 (1H, d), 7.55 (1H, s); MS m/z (ES ⁺) 318 (MH ⁺)
99	Example 76			HCl salt: δ_H (CD ₃ OD, 300 MHz) 2.39 (3H, s), 2.47 (3H, s), 2.85 (6H, s), 4.32 (2H, s), 4.44 (2H, s), 6.80-6.86 (3H, m), 7.21 (1H, d), 7.35 (1H, d), 8.08 (1H, s); MS m/z (ES ⁺) 449 (MH ⁺), (ES ⁻) 447 (M-H ⁺)
100	Example 102			δ_H (CD ₃ OD, 400 MHz) 2.26 (6H, s), 3.58 (2H, s), 6.97 (1H, d), 7.35 (1H, d), 7.46 (1H, dd), 7.54 (1H, d), 7.80 (1H, d), 8.03 (2H, m), 8.20 (1H, d), 8.74 (1H, d); MS m/z (TS ⁺) 322 (MH ⁺)

Example 94 was also prepared as follows.

A solution of the product from Preparation 30 (200 g, 0.78 mol) in DCM (1.4 L) was added to THF (1.4 L). To this mixture was added dimethylamine hydrochloride (69.5 g, 0.85 mol) and triethylamine (235 g, 2.33 mol) successively. The temperature was adjusted to 20 °C and after 3 h sodium triacetoxyborohydride (246 g, 1.16 mol) was added (After 20 h, if the reaction has completed, continue with work up; otherwise see note below). Dichloromethane (2 L) was added and a solution of 8% sodium bicarbonate (0.9 L) was added over 0.5 h. The layers were separated and the organic layer washed with water (1 L). The layers were again separated and the organic layer was concentrated. Ethyl acetate (0.27 L) was added and the solvent removed replacing with

fresh ethyl acetate (800 ml). The solution was then cooled to below 5 °C and 7.02 M HCl/IPA (0.117 L, 0.82 mol) added whilst the temperature was maintained below 10 °C. After stirring for 1 h at below 5 °C, the slurry was filtered, washed with ethyl acetate (3 x 0.2 L) and dried in a vacuum oven at 50 °C overnight to give the desired product as a powdery solid (141.5 g, 56%). [Note: if reaction hasn't completed after 20h. Add another portion of dimethylamine hydrochloride (13g, 0.16mol) and triethylamine (43.4g, 0.43mol) successively. After 2h at room temperature add sodium triacetoxyborohydride (46g, 0.22mol). Leave for a further 20h and then work up as above].

- 10 Compounds of formula II, i.e. compounds of general formula I where R^2 is methyl, R^4 is hydrogen and R^5 is $-C(=O)NH_2$, shown in Table 11 were prepared according to Example 79 from the precursors indicated.



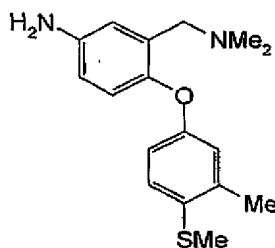
15

Table 11

Example	Precursor	R^1		data
101	Example 92	Me		δ_H (CDCl ₃ , 300 MHz) 2.30 (6H, s), 2.35 (3H, s), 2.46 (3H, s), 3.58 (2H, s), 5.60-5.80 (1H, brs), 6.00-6.20 (1H, brs), 6.32 (3H, m), 7.19 (1H, m), 7.71 (1H, d), 7.90 (1H, s); MS m/z (TS ⁺) 331 (MH ⁺)
102	Example 49	H		δ_H (CDCl ₃ , 400 MHz) 2.43 (3H, s), 3.84 (2H, s), 6.94 (1H, d), 7.20 (1H, d), 7.34-7.39 (1H, m), 7.43 (1H, dd), 7.70 (1H, d), 7.91 (1H, s), 7.99 (1H, d), 8.09 (1H, d), 8.82 (1H, d); MS m/z (ES ⁺) 309 (MH ⁺)

EXAMPLE 103

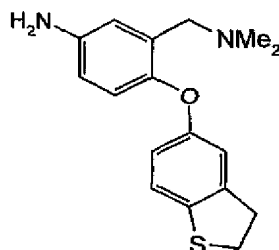
N-[5-Amino-2-[3-methyl-4-(methylsulfanyl)phenoxy]benzyl]-*N,N*-dimethylamine



A mixture of the nitro compound of Example 27 (2.0 g, 6 mmol), Fe powder (2.51 g, 44.9 mmol) and CaCl₂ (300 mg, 2.7 mmol) in EtOH (20 mL) and water (4 mL) was heated at reflux for 20 h. After cooling to room temperature the solvent was removed *in vacuo* and the residue was partitioned between brine (100 mL) and ether (100 mL). The aqueous layer was extracted with ether (50 mL) and the combined organic layers were dried (MgSO₄) and evaporated to give the product (1.47 g; 81%) as an orange oil; δ_H (CDCl₃, 300 MHz) 2.22 (6H, s), 2.32 (3H, s), 2.40 (3H, s), 3.33 (2H, s), 6.59 (1H, dd), 6.60-6.75 (2H, m), 6.78 (1H, dd), 6.94 (1H, s), 7.10-7.20 (3H, m); MS *m/z* (ES⁺) 303 (MH⁺).

EXAMPLE 104

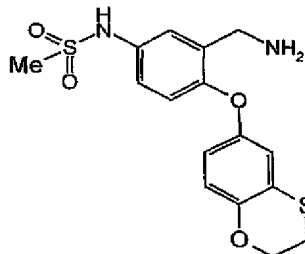
N-[5-Amino-2-(2,3-dihydro-1-benzothien-5-yloxy)benzyl]-*N,N*-dimethylamine



The title compound was prepared from the nitro compound of Example 28 by the method of Example 103; δ_H (CDCl₃, 400 MHz) 2.20 (6H, s), 3.16 (2H, t), 3.30 (4H, m), 3.54 (2H, br), 6.53 (1H, dd), 6.60 (1H, d), 6.71 (2H, m), 6.79 (1H, d), 7.01 (1H, d); MS *m/z* (ES⁺) 301 (MH⁺).

EXAMPLE 105

N-[3-(Aminomethyl)-4-(2,3-dihydro-1,4-benzoxathiin-6-yloxy)phenyl]-methanesulfonamide



5

The nitrile of Preparation 95 (720 mg, 1.99 mmol) was dissolved in a 1M solution of BH_3 .THF in THF (10 mL, 10 mmol) and the mixture was heated at reflux for 3 h. After cooling to room temperature the reaction was quenched by the cautious addition of MeOH (10 mL). The solvent was evaporated, the residue was treated with 6M HCl (10 mL) and heated at reflux for 1 h. After cooling, the mixture was basified with 2M NaOH and the pH was adjusted to 7 with sat aq NH_4Cl . The mixture was extracted with EtOAc (3×50 mL) and DCM (2×50 mL) and the combined organic layers were dried (MgSO_4) and evaporated to give a beige foam (685 mg, 94%) which was used without further purification; δ_{H} (CDCl_3 , 400 MHz) 3.00 (3H, s), 3.13 (2H, m), 3.87 (2H, s), 4.40 (2H, m), 6.62 (1H, d), 6.67 (1H, s), 6.79 (2H, d), 7.08 (1H, d), 7.25 (1H, d); MS m/z (TS^+) 367 (MH^+).

Compounds of formula Ij, i.e. compounds of general formula I where R^1 , R^2 and R^4 are hydrogen and R^5 is $-\text{NR}^8-\text{SO}_2\text{Me}$, shown in Table 12 were prepared according to Example 105 from the precursors indicated

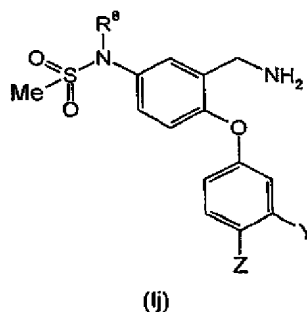
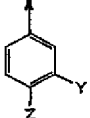
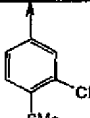
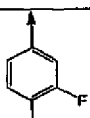
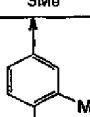
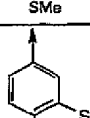
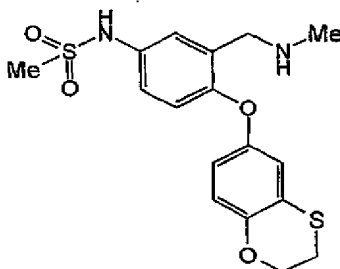


Table 12

Example	Precursor		R ⁸	data
106	Prep 96		H	δ_H (CDCl ₃ , 300 MHz) 2.47 (3H, s), 3.02 (3H, s), 3.08 (3H, br), 3.85 (2H, s), 6.87 (2H, m), 6.99 (1H, d), 7.15 (1H, dd), 7.20 (1H, d), 7.30 (1H, d); MS <i>m/z</i> (ES ⁺) 371 (M-H ⁺)
107	Prep 97		H	Used crude in a subsequent step: δ_H (CD ₃ OD, 400 MHz) 2.37 (3H, s), 2.95 (3H, s), 3.75 (2H, s), 6.58 (1H, d), 6.71 (2H, m), 6.89 (1H, d), 7.15 (1H, dd), 7.28 (1H, obs)
108	Prep 100		Me	Used crude in a subsequent step: δ_H (CDCl ₃ , 300 MHz) 2.36 (3H, s), 2.46 (3H, s), 2.90 (3H, s), 3.36 (3H, s), 3.93 (2H, s), 6.83 (3H, m), 7.20 (2H, m), 7.42 (1H, d).
109	Prep 99		H	δ_H (CD ₃ OD, 400 MHz) 2.24 (3H, s), 2.40 (3H, s), 2.97 (3H, s), 3.80 (2H, s), 6.60 (1H, d), 6.81-6.87 (2H, m), 7.08-7.17 (2H, m), 7.29 (1H, d); MS <i>m/z</i> (ES ⁺) 353 (MH ⁺), (ES ⁻) 351 (M-H ⁺)

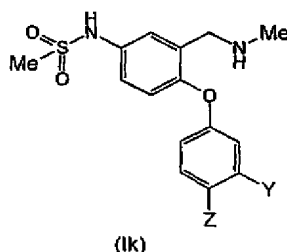
EXAMPLE 110

- 5 N-[4-(2,3-Dihydro-1,4-benzoxathiin-6-yloxy)-3-[(methylamino)methyl]phenyl]-methanesulfonamide



- Dicyclohexylcarbodiimide (460 mg, 2.23 mmol) was added to a solution of pentafluorophenol (413 mg, 2.24 mmol) in ether (10 mL) followed by formic acid (95 μ L, 2.5 mmol). The mixture was stirred for 2 h and then filtered, washing the residue with ether. The filtrate was concentrated to ~5 mL and a solution of the primary amine of Example 105 (411 mg, 1.1 mmol) in DCM (10 mL) was added. The mixture was stirred for 16 h then concentrated to an oily residue. This crude oil was taken up in a solution of BH₃.THF in THF (1M, 20 mL, 20 mmol) and heated at reflux for 1.5 h under N₂. After cooling to room temperature the reaction was quenched by the cautious addition of MeOH (10 mL) and then concentrated *in vacuo*. The oily residue was treated with 6M

- HCl and heated at reflux for 30 min. After cooling to room temperature the mixture was basified with aq K_2CO_3 and extracted with DCM (3 \times). The combined organic extracts were dried ($MgSO_4$) and evaporated. The residue was purified by column chromatography [SiO_2 ; 90:10:1 (DCM/ MeOH/ 880 NH_3)] to give a colourless oil which
- 5 was taken up in EtOAc (20 mL) and treated with 1M ethereal HCl (2 mL). After stirring for 1.5 h the solid was collected by filtration to give the title product (282 mg, 60%); δ_H (CD_3OD , 400 MHz) 2.78 (3H, s), 2.98 (3H, s), 3.18 (2H, m), 4.29 (2H, s), 4.39 (2H, m), 6.74 (1H, d), 6.80-6.90 (3H, m), 7.22 (1H, d), 7.44 (1H, s); MS m/z (TS^+) 381 (MH^+).
- 10 Compounds of formula Ik, i.e. compounds of general formula I where R^1 and R^4 are hydrogen, R^2 is methyl and R^5 is $-NHSO_2Me$, shown in Table 13 were prepared according to Example 110 from the precursors indicated.

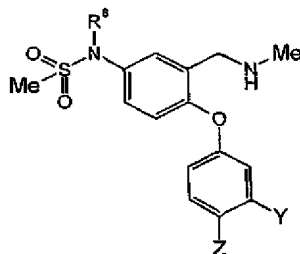


15

Table 13

Example	Precursor		data
111	Example 107		δ_H ($CDCl_3$, 400 MHz) 2.40 (6H, s), 2.99 (3H, s), 3.70 (2H, s), 6.64 (2H, t), 6.88 (1H, d), 7.15 (1H, d), 7.25 (2H, s); MS m/z (TS^+) 371 (MH^+)
112	Example 106		HCl salt: δ_H (CD_3OD , 400 MHz) 2.55 (3H, s), 3.82 (3H, s), 3.04 (3H, s), 4.32 (2H, s), 6.97 (1H, d), 7.11 (1H, d), 7.23 (1H, s), 7.30 (1H, d), 7.39 (1H, d), 7.56 (1H, s); MS m/z (TS^+) 387 (MH^+)
113	Example 109		HCl salt: δ_H (CD_3OD , 400 MHz) 2.24 (3H, s), 2.39 (3H, s), 2.76 (3H, s), 2.93 (3H, s), 4.25 (2H, s), 6.69 (1H, d), 6.82 (1H, d), 6.93 (1H, s), 7.17 (1H, d), 7.21 (1H, d), 7.43 (1H, s); MS m/z (ES^+) 367 (MH^+), (ES^-) 365 ($M-H^+$)

Compounds of formula Im, i.e. compounds of general formula I where R¹ and R⁴ are hydrogen, R² is methyl and R⁵ is -NR⁶SO₂Me, shown in Table 14 were prepared according to Example 110 from the precursors indicated.

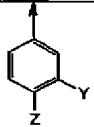
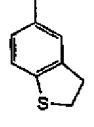


(Im)

5

Table 14

Example	Precursor	R ⁶		data
114	Prep 85	H		HCl salt: δ_H (CDCl ₃ , 400 MHz) 2.09 (2H, m), 2.73 (3H, s), 2.88 (4H, t), 3.00 (3H, s), 4.21 (2H, s), 6.80 (2H, m), 6.88 (1H, s), 7.19 (1H, d), 7.34 (1H, d), 7.75 (1H, s); MS <i>m/z</i> (TS ⁺) 347 (MH ⁺)
115	Prep 84	H		HCl salt: δ_H (d ₆ -DMSO, 400 MHz) 2.20 (3H, s), 2.40 (3H, s), 2.55 (3H, s), 2.97 (3H, s), 4.08 (2H, s), 6.80 (1H, d), 6.87 (1H, d), 6.91 (1H, s), 7.14 (1H, d), 7.20 (1H, d), 7.39 (1H, s); MS <i>m/z</i> (TS ⁺) 367 (MH ⁺)
116 ^a	Prep 88	Me		δ_H (CDCl ₃ , 300 MHz) 2.17 (3H, s), 2.37 (3H, s), 2.48 (3H, s), 2.62 (3H, s), 2.97 (3H, s), 3.34 (3H, s), 4.23 (2H, s), 6.79 (1H, d), 6.94 (2H, s), 7.35 (2H, m), 7.81 (1H, s); MS <i>m/z</i> (TS ⁺) 381 (MH ⁺)
117	Prep 89			HCl salt: δ_H (CDCl ₃ , 400 MHz) 2.29 (3H, s), 2.39 (3H, s), 2.42 (3H, s), 2.94 (3H, s), 3.60 (2H, t), 3.74 (2H, t), 3.79 (2H, s), 6.78 (3H, m), 7.14 (2H, m), 7.41 (1H, s); MS <i>m/z</i> (TS ⁺) 410 (MH ⁺)
118	Prep 87	H		δ_H (CDCl ₃ , 400 MHz) 2.42 (3H, s), 2.58-2.79 (2H, br), 2.94 (3H, s), 3.08 (2H, m), 3.71 (2H, s), 4.38 (2H, m), 6.39 (1H, s), 6.47 (1H, d), 6.82 (1H, d), 6.94 (1H, d), 7.07 (1H, d), 7.18 (1H, s); MS <i>m/z</i> (TS ⁺) 381 (MH ⁺)

Example	Precursor	R ⁸		data
119	Prep 86	H		δ_H (CD ₃ OD, 400 MHz) 2.80 (3H, s), 3.00 (3H, s), 3.27 (2H, m), 3.40 (2H, m), 4.28 (2H, m), 6.85 (2H, m), 7.00 (1H, s), 7.20 (1H, d), 7.24 (1H, dd), 7.47 (1H, d); MS m/z (TS ⁺) 365 (MH ⁺)

^a – Also made from Example 108 by the method of Example 110.

Compounds of formula In, i.e. compounds of general formula I where R¹ and R² are methyl, R⁴ is hydrogen, and R⁵ is -NR⁸SO₂Me, shown in Table 15 were prepared

5 according to Example 12 from the precursors indicated.

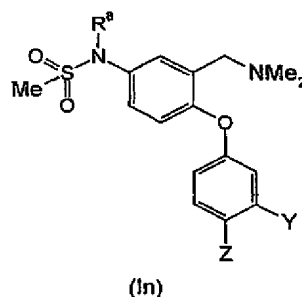
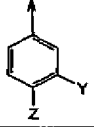
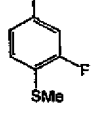
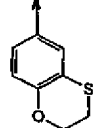
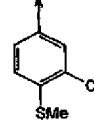
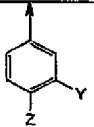
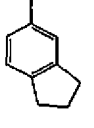
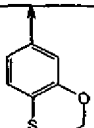

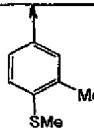
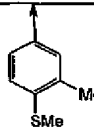
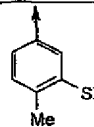


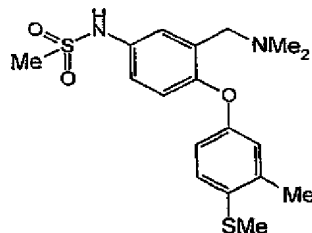
Table 15

Example	Precursor	R ⁸		Data
120	Example 111	H		HCl salt: δ_H (CD ₃ OD, 400 MHz) 2.42 (3H, s), 2.89 (6H, s), 2.98 (3H, s), 4.37 (2H, s), 6.88 (2H, m), 6.97 (1H, d), 7.28 (1H, d), 7.39 (1H, t), 7.48 (1H, s); MS m/z (TS ⁺) 385 (MH ⁺)
121 (from primary amine)	Example 105	H		δ_H (CDCl ₃ , 400 MHz) 3.00 (3H, s), 3.13 (2H, m), 3.87 (2H, s), 4.40 (2H, m), 6.62 (1H, d), 6.67 (1H, s), 6.79 (2H, d), 7.08 (1H, d), 7.25 (1H, d); MS m/z (TS ⁺) 367 (MH ⁺)
122 (from primary amine)	Example 106	H		HCl salt: δ_H (CD ₃ OD, 400 MHz) 2.49 (3H, s), 2.93 (6H, s), 3.00 (3H, s), 4.41 (2H, s), 6.95 (1H, d), 7.07 (1H, d), 7.21 (1H, s), 7.33 (2H, m), 7.54 (1H, s); MS m/z (TS ⁺) 395 (MH ⁺)

Example	Precursor	R ^a		Data
123	Example 114	H		HCl salt: δ_H (CDCl ₃ , 400 MHz) 2.12 (2H, m), 2.81 (6H, s), 2.91 (4H, t), 3.13 (3H, s), 4.25 (2H, s), 6.73 (1H, d), 6.83 (2H, m), 7.10 (1H, d), 7.39 (1H, d), 7.90 (1H, s); MS m/z (TS ⁺) 360 (MH ⁺)
124	Example 118	H		δ_H (CDCl ₃ , 400 MHz) 2.22 (6H, s), 2.98 (3H, s), 3.07 (2H, m), 3.41 (2H, s), 4.38 (2H, m), 6.36 (1H, s), 6.45 (1H, d), 6.86 (1H, d), 6.92 (1H, d), 7.12 (1H, d), 7.27 (1H, s); MS m/z (TS ⁺) 395 (MH ⁺)
125	Example 117			HCl salt: δ_H (CDCl ₃ , 300 MHz) 2.38 (3H, s), 2.48 (3H, s), 2.86 (6H, brs), 3.15 (3H, s), 3.73 (2H, brs), 3.87 (2H, brs), 4.35 (2H, brs), 6.82 (3H, brs), 7.20 (2H, m), 7.41 (1H, d); MS m/z (TS ⁺) 425 (MH ⁺)
126 (from primary amine)	Example 108	Me		HCl salt: δ_H (CD ₃ OD, 400 MHz) 2.29 (3H, s), 2.43 (3H, s), 2.89 (3H, s), 2.91 (6H, s), 3.26 (3H, s), 4.42 (2H, s), 6.84 (1H, d), 6.97 (2H, m), 7.27 (1H, d), 7.47 (1H, dd), 7.60 (1H, d); MS m/z (TS ⁺) 395 (MH ⁺)
127 (from primary amine)	Example 109	H		HCl salt: δ_H (CD ₃ OD, 400 MHz) 2.27 (3H, s), 2.42 (3H, s), 2.94 (6H, s), 2.99 (3H, s), 4.42 (2H, s), 6.77 (1H, d), 6.89 (1H, d), 6.99 (1H, s), 7.19 (1H, d), 7.28 (1H, dd), 7.50 (1H, s); MS m/z (TS ⁺) 381 (MH ⁺), (ES ⁺) 381 (MH ⁺), (ES ⁻) 379 (M-H ⁺)

EXAMPLE 128

N-[3-[(Dimethylamino)methyl]-4-[3-methyl-4-(methylsulfanyl)phenoxy]phenyl]methanesulfonamide



5

Methanesulfonyl chloride (371 μ L, 4.79 mmol) was added to a solution of the aniline of Example 103 (725 mg, 2.4 mmol) and Et₃N (1 mL, 7.17 mmol) in DCM (10 mL) at 0°C. After stirring at 0°C for 1 h the reaction was allowed to warm to room temperature before the solvent was removed *in vacuo*. 2M NaOH (10 mL) was added to the residue and the mixture was stirred overnight. The resulting clear solution was neutralised by the addition

10

of sat aq NH_4Cl and extracted with DCM (2×30 mL). The combined organic layers were dried (MgSO_4) and evaporated to give an oil. This was taken up in EtOAc (10 mL), the HCl salt was precipitated by the addition of 1M ethereal HCl and the product (669 mg, 67%) was collected by filtration; δ_{H} (d_6 -DMSO, 400 MHz) 2.23 (3H, s), 2.42 (3H, s), 2.75 (6H, s), 3.04 (3H, s), 4.38 (2H, s), 6.84 (1H, d), 6.93 (1H, d), 6.98 (1H, s), 7.17-7.25 (2H, m), 7.50 (1H, s); MS m/z (ES^+) 381 (MH^+).

Compounds of formula Ip, i.e. compounds of general formula I where R^1 and R^2 are methyl, R^4 is hydrogen, and R^5 is $-\text{NHSO}_2\text{R}^9$, shown in Table 16 were prepared according to Example 128 from the precursors indicated.

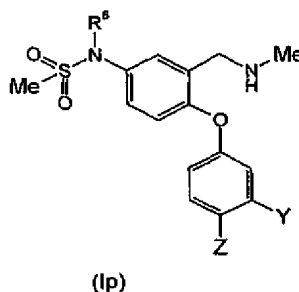


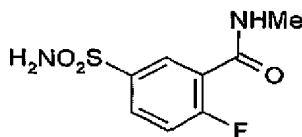
Table 16

Example	Precursor	R^9		data
129	Example 104	Me		HCl salt: δ_{H} (CD_3OD , 400 MHz) 2.92 (6H, s), 2.99 (3H, s), 3.26 (2H, t), 3.40 (2H, t), 4.41 (2H, s), 6.88 (2H, d), 7.00 (1H, s), 7.10 (1H, d), 7.27 (1H, d), 7.50 (1H, s); MS m/z (TS^+) 381 (MH^+)
130	Example 103	Et		HCl salt: δ_{H} (d_6 -DMSO, 400 MHz) 1.21 (3H, t), 2.23 (3H, s), 2.42 (3H, s), 2.74 (6H, s), 3.16 (2H, q), 4.26 (2H, s), 6.92 (1H, d), 6.92 (1H, d), 6.98 (1H, s), 7.18-7.25 (2H, m), 7.51 (1H, s); MS m/z (ES^+) 395 (MH^+)

PREPARATIONS

PREPARATION 1

5-(Aminosulfonyl)-2-fluoro-N-methylbenzamide



5

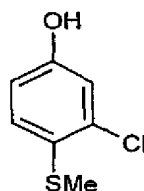
To a solution of 5-(aminosulfonyl)-2-fluorobenzoic acid [prepared according to *Chem. Pharm. Bull.* 1995, 43, 582-7] (22.98 g, 105 mmol) in THF (500 mL) at room temperature under nitrogen was added carbonyldiimidazole (17 g, 105 mmol). After stirring for 2.25 h a solution of methylamine in THF (2M, 70 mL, 140 mmol) was added dropwise and the reaction was allowed to stir for 18 h. The crude reaction mixture was concentrated to a low volume and EtOAc (150 mL) was added to the resulting thick oil. This mixture was stirred and a granular precipitate formed which was collected by filtration. This crude product, contaminated with imidazole, was suspended in DCM (300 mL) and heated at reflux for 5 h. After cooling to room temperature the mixture was filtered to give the desired product (19.8 g, 81%) containing <2% w/w imidazole; ^1H NMR δ_{H} (300 MHz, d_4 -MeOH) 2.97 (3H, s), 7.40 (1H, t), 8.05 (1H, m), 8.29 (1H, d); MS m/z (TS^+) 250 (MNH_4^+).

10

15

PREPARATION 2

3-Chloro-4-(methylsulfonyl)phenol



20

(i) Preparation of 2-chloro-1-(methylsulfonyl)-4-nitrobenzene

To a solution of 4-fluoro-3-chloronitrobenzene (27 g, 156 mmol) in DMF (150 mL) at room temperature was added 5-*tert*-butyl-4-hydroxy-2-methylphenyl sulfide (100 mg) followed by sodium thiomethoxide (NaSMe) (10 g, 143 mmol) and the reaction was stirred for 6h. The DMF was removed *in vacuo* and the residue was partitioned between ether (1 L) and water (1 L). The ether layer was washed with water (1 L) and brine (1 L), dried (MgSO_4) and the solvent was removed under reduced pressure. The residue was purified by column chromatography (SiO_2 ; DCM: pentane 1:5 increasing polarity to 3:7)

25

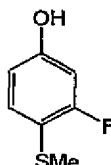
to give the title compound (15.22 g, 49%) as a yellow solid; δ_{H} (400 MHz, CDCl_3) 2.53 (3H, s), 7.20 (1H, d), 8.09 (1H, dd), 8.20 (1H, d).

(ii) Preparation of 3-chloro-4-(methylsulfanyl)aniline

To a mixture of the above compound (14.08 g, 69 mmol) in acetic acid (300 mL) and
5 water (60 mL) was added Fe powder (23 g, 412 mmol) and the reaction mixture was
swirled until all the starting material had dissolved. The mixture was left to stand for 1.5 h
and the acetic acid was then removed under reduced pressure. The residue was taken
up in sat NaHCO_3 (aq) (500 mL) and EtOAc (500 mL) and filtered through Arbocel®. The
layers were separated, the aqueous phase was extracted with EtOAc (300 mL) and the
10 combined organics were washed with brine, dried (MgSO_4) and the solvent was removed
in vacuo to give the title compound (11.52 g, 96%) as a beige solid; δ_{H} (400 MHz, CDCl_3)
2.38 (3H, s), 3.66 (2H, br), 6.53 (1H, dd), 6.70 (1H, d), 7.12 (1H, d); MS m/z (ES^+) 174
(MH^+).

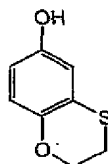
(iii) Preparation of 3-chloro-4-(methylsulfanyl)phenol

15 The above aniline (11.5 g, 66.2 mmol) was dissolved in the minimum THF (~15 mL) and
water (500 mL) was added with vigorous stirring, followed by conc H_2SO_4 (25 mL). The
mixture was cooled in an ice-water bath and a solution of NaNO_2 (5.0 g, 72.5 mmol) in
iced water (10 mL), was added via pipette under the surface of the reaction mixture. The
reaction was stirred at 0°C for 1.5 h and the resulting yellow/brown solution was
20 decanted from the remaining solid into a dropping funnel containing ice (~200 g). This
solution was added at a steady rate over 7 min to a vigorously stirred mixture of
 $\text{Cu}(\text{NO}_3)_2$ (230 g, 0.99 mol) and Cu_2O (8.52 g, 67.4 mmol) in water (1 L) at room
temperature. After the addition was complete the mixture was stirred for a further 15 min
before being extracted with ether (500 mL). The residual red/brown solid in the reaction
25 flask was taken up in MeOH (100 mL) and diluted with ether (300 mL) before being
poured into the aqueous layer from above. The ether layer was separated and the
combined organic layers were extracted with 1M NaOH (3 x 100 mL). The aqueous
extracts were acidified with conc. HCl and then extracted with ether (2 x 150 mL). The
ether layers were then washed with brine, dried (MgSO_4) and the solvent was removed
30 *in vacuo* to give the phenol (5.465 g, 47%) as a brown crystalline solid; δ_{H} (400 MHz,
 CDCl_3) 2.44 (3H, s), 5.08 (1H, br), 6.77 (1H, d), 6.93 (1H, d), 7.18 (1H, d); MS m/z (ES^-)
173 (M-H^+).

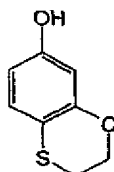
PREPARATION 33-Fluoro-4-(methylsulfanyl)phenol

This compound was prepared using a similar method to that described above for

- 5 Preparation 2 starting from commercially available 3,4-difluoronitrobenzene; δ_H ($CDCl_3$, 300 MHz) 2.40 (3H, s), 5.03 (1H, br), 6.60 (2H, m), 7.27 (1H, m obscured); MS m/z (ES^+) 157 ($M-H^+$).

PREPARATION 410 2,3-Dihydro-1,4-benzoxathiin-6-ol

- 1,2-Dibromoethane (2.3 mL, 26.7 mmol) and K_2CO_3 (8.21 g, 59.4 mmol) were slurried in acetone (250 mL) and a solution of 2-sulfanyl-1,4-benzenediol (prepared according to *J. Org. Chem.* 1990, 55, 2736) (4.22 g, 29.7 mmol) in acetone (50 mL) was added over 4 h
- 15 to the stirred mixture. Once the addition was complete stirring was continued for a further 10 h before the solvent was removed *in vacuo*. The residue was partitioned between water (50 mL) and EtOAc (50 mL), the aqueous layer was extracted with EtOAc (50 mL) and the combined organic layers were dried ($MgSO_4$) and evaporated.
- Purification of the residue by column chromatography [SiO_2 ; 9:1 (pentane/EtOAc)] gave
- 20 the title compound (2.48 g, 55%) as a pale orange oil; δ_H ($CDCl_3$, 400 MHz) 3.08 (2H, m), 4.31 (2H, m), 4.44 (1H, s), 6.42 (1H, d), 6.49 (1H, s), 6.66 (1H, d); MS m/z (ES^+) 167 ($M-H^+$).

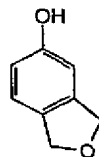
PREPARATION 525 2,3-Dihydro-1,4-benzoxathiin-7-ol

The title compound was prepared in a similar manner to the compound of Preparation 4 starting from 4-sulfanyl-1,3-benzenediol (prepared according to *J. Org. Chem.* 1979, 26, 4971-4973); δ_H ($CDCl_3$, 400 MHz) 3.05 (2H, t), 4.37 (2H, t), 6.32 (1H, s), 6.35 (1H, d), 6.84 (1H, d); MS m/z (TS^+) 169 (MH^+).

5

PREPARATION 6

1,3-Dihydro-2-benzofuran-5-ol

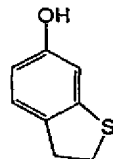


1,3-Dihydro-2-benzofuran-5-amine (prepared according to US4000286) (2.7 g, 20 mmol) was dissolved in a mixture of water (300 mL) and conc. H_2SO_4 (21 mL), cooled to $0^\circ C$ and $NaNO_2$ (1.43 g, 20.7 mmol) in water (10 mL) was added over 15 min. After stirring at $0^\circ C$ for 1 h the mixture was allowed to stir at $10^\circ C$ for 30 min and urea was added until a negative test with starch/KI paper was observed. The solution was then poured over 2 min into a mixture of water (180 mL) and conc. H_2SO_4 (12.6 mL) at $90^\circ C$ and stirred at 15 this temperature for 1.5 h. The hot mixture was filtered then allowed to cool to room temperature. The aqueous mixture was extracted with EtOAc (2×100 mL) and the combined organic layers were dried ($MgSO_4$) and evaporated to give the title phenol (974 mg, 36%) as a cream solid; δ_H ($CDCl_3$, 400 MHz) 5.03 (4H, s), 6.71 (2H, m), 7.08 (1H, d).

20

PREPARATION 7

2,3-Dihydro-1-benzothiophen-6-ol



(i) Preparation of 2,3-dihydro-1-benzothiophen-6-ol 1,1-dioxide

25 A suspension of 2,3-dihydro-1-benzothiophen-6-amine 1,1-dioxide [prepared according to *J. Am. Chem. Soc.* 1955, 77, 5939] (15.73 g, 85.8 mmol) in water (500 mL) and conc. H_2SO_4 (35 mL) was warmed until solution was achieved. The mixture was cooled to $0^\circ C$ and a solution of $NaNO_2$ (6.22 g, 90 mmol) in water (15 mL) was then added over 5 min. The reaction was stirred at $0^\circ C$ for 1 h then urea was added, to remove excess nitrite,

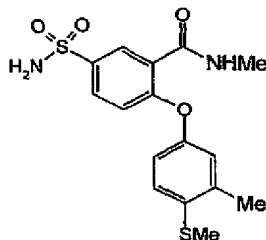
until a negative test with starch/KI paper was obtained. The mixture was allowed to warm to room temperature then added with stirring to a mixture of conc. H_2SO_4 (55 mL) and water (750 mL) at 90°C . The reaction was re-heated to 90°C and stirred at this temperature for 30 min. The hot reaction mixture was filtered through Arbocel® then stirred at room temperature overnight. The aqueous mixture was extracted with ether (2.5 L) and then EtOAc (5×500 mL) and the combined organic layers were dried (MgSO_4) and evaporated to give the desired phenol (12.7 g, 80%) which was used without further purification; δ_{H} (CDCl_3 , 400 MHz) 3.30 (2H, m), 3.50 (2H, m), 7.05 (1H, m), 7.14 (1H, s), 7.23 (1H, m); MS m/z (ES^-) 183 ($\text{M}-\text{H}^+$).

10 (ii) Preparation of 2,3-dihydro-1-benzothiophen-6-ol

A solution of the sulfone from stage (i) (4.84 g, 26.3 mmol) in toluene (100 mL) and THF (70 mL) was added to a solution of DIBAL in toluene (1M, 100 mL, 100 mmol) and the mixture was then heated at reflux for 16 h. After cooling to room temperature EtOH (75 mL) was added cautiously followed by water (100 mL) with stirring. 6M HCl was added to the resulting thick suspension and the organic layer was separated. The aqueous layer was extracted with EtOAc (3×150 mL) and the combined organic layers were dried (MgSO_4) and evaporated to a beige solid. Purification by column chromatography [SiO_2 ; DCM/ MeOH/ 880 NH_3 (97:3:0.25) increasing polarity to (95:5:0.5)] afforded the desired title phenol as a beige solid (1.85 g, 53%); δ_{H} (CD_3OD , 400 MHz) 3.13 (2H, t), 3.30 (2H, m), 6.41 (1H, d), 6.60 (1H, s), 6.98 (1H, d); MS m/z (ES^-) 151 ($\text{M}-\text{H}^+$).

PREPARATION 8

5-(Aminosulfonyl)-2-[3-methyl-4-(methylsulfonyl)phenoxy]-N-methylbenzamide



25 The fluoroamide of Preparation 1 (732 mg, 3.15 mmol) was treated with 4-(methylthio)-*m*-cresol (commercially available) (535 mg, 3.47 mmol) and potassium carbonate (457 mg, 3.31 mmol) in DMF (10 mL). The mixture was heated at 100°C for 5 hours. The solvent was removed by evaporation under reduced pressure and the residue was treated with 2M HCl (10 mL). The resulting suspension was extracted several times with
30 dichloromethane. The combined dichloromethane layers contained a suspension and

were evaporated to a solid residue. The residue was triturated with ether (5 mL) and the remaining solid was washed with ether (3x10 mL) to give an off-white solid (765 mg, 66%). δ_H (300 MHz, d_6 -DMSO) 2.28 (3H, s), 2.48 (3H, s), 2.70 (3H, d), 6.90 (1H, d), 7.02 (1H, d), 7.03 (1H, s), 7.30 (1H, d), 7.35 (2H, s), 7.79 (1H, d), 8.10 (1H, d), 8.30 (1H, m);

5 MS m/z (TS^+) 367 (MH^+), 385 (MNH_4^+).

PREPARATIONS 9-18

Compounds of formula Va, i.e. compounds of general formula V where T is -C(=O)NHMe, R^4 is hydrogen and R^5 is -SO₂NH₂, shown in Table 17 were prepared

10 according to Preparation 8 using the sulfonamide of Preparation 1 and the phenol indicated.

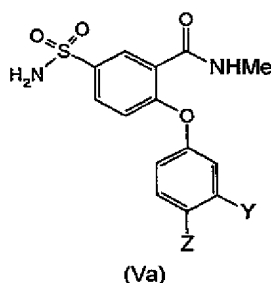
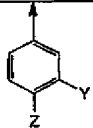
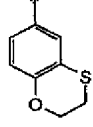
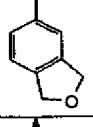
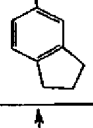
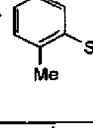
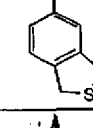
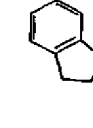
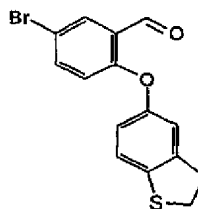


Table 17

Preparation	Precursor phenol		data
9	Synth. Commun. 1991, 21, 959-964		δ_H (d_6 -DMSO, 400 MHz) 2.80 (3H, d), 3.20 (2H, t), 3.40 (2H, t), 6.90 (1H, m), 7.05 (1H, s), 7.25 (1H, d), 7.35 (1H, s), 7.80 (1H, m), 8.10 (1H, s), 8.30 (1H, brs); MS m/z (TS^+) 365 (MH^+)
10	Prep 5		δ_H (CD_3OD , 400 MHz) 2.92 (3H, s), 3.17 (2H, m), 4.41 (2H, m), 6.60-6.70 (2H, m), 6.97 (1H, d), 7.18 (1H, d), 7.90 (1H, d), 8.31 (1H, s); MS m/z (TS^+) 381 (MH^+)
11	Prep 3		δ_H (CD_3OD , 400 MHz) 2.43 (3H, s), 2.97 (1H, s), 6.89 (2H, m), 7.00 (1H, d), 7.39 (1H, br), 7.88 (1H, brd), 8.23 (1H, s); MS m/z (ES^+) 371 (MH^+)
12	Prep 2		δ_H (CD_3OD , 400 MHz) 2.85 (3H, s), 2.99 (3H, s), 6.99 (1H, d), 7.09 (1H, d), 7.22 (1H, s), 7.37 (1H, d), 7.92 (1H, d), 8.28 (1H, s); MS m/z (ES^+) 387 (MH^+)

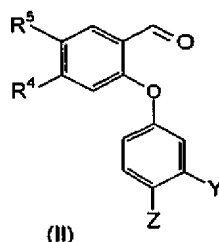
Preparation	Precursor phenol		data
13	Prep 4		δ_H (CD ₃ OD, 400 MHz) 2.87 (3H, brs), 3.13 (2H, brs), 4.37 (2H, brs), 6.73 (1H, brs), 6.82 (3H, m), 7.82 (1H, s), 8.28 (1H, brs); MS m/z (ES ⁺) 381 (MH ⁺)
14	Prep 6		δ_H (d ₆ -DMSO, 400 MHz) 2.79 (3H, s), 4.98 (4H, brs), 6.92 (1H, d), 7.04 (1H, d), 7.09 (1H, s), 7.37 (3H, m), 7.79 (1H, m), 8.10 (1H, s), 8.30 (1H, s); MS m/z (TS ⁺) 349 (MH ⁺)
15	Commercial		δ_H (CD ₃ OD, 400 MHz) 2.08 (2H, m), 2.90 (7H, m), 6.84 (2H, m), 6.97 (1H, s), 7.23 (1H, d), 7.81 (1H, d), 8.31 (1H, s); MS m/z (TS ⁺) 347 (MH ⁺)
16	<i>Tetrahedron</i> 1982, 38, 2721 & <i>Synthesis</i> 1982, 475		Product used without purification
17	Prep 101		δ_H (CD ₃ OD, 400 MHz) 2.88 (3H, s), 4.20 (4H, s), 6.89 (1H, d), 6.97 (1H, d), 7.01 (1H, s), 7.30 (1H, d), 7.84 (1H, d), 8.28 (1H, s); MS m/z (TS ⁺) 382 (MNH ₄ ⁺)
18	Prep 7		δ_H (DMSO-d ₆ , 400 MHz) 2.78 (3H, d), 3.23 (2H, m), 3.40 (2H, m), 6.75 (1H, dd), 6.90 (1H, d), 7.02 (1H, s), 7.27 (1H, d), 7.34 (1H, d), 7.80 (1H, d), 8.10 (1H, s), 8.26 (1H, br, d); MS m/z (ES ⁻) 363 (M-H ⁺)

PREPARATION 19**5-Bromo-2-(2,3-dihydro-1-benzothien-5-yloxy)benzaldehyde**

- 5 A mixture of 5-bromo-2-fluorobenzaldehyde (1.08 g, 5.32 mmol), 5-hydroxy-2,3-dihydrobenzothiophene (prepared as described in *Synth. Commun.* 1991, 21, 959-964) (808 mg, 5.31 mmol) and K₂CO₃ (1.47 g, 10.6 mmol) in DMF (5 mL) was heated at 90°C for 16 h. After cooling to room temperature the mixture was partitioned between water (50 mL) and ether (50 mL), the aqueous layer being extracted with ether (50 mL).
- 10 The combined organic extracts were washed with water (50 mL), dried (MgSO₄) and evaporated. The residue was purified by column chromatography [SiO₂; 9:1

(pentane/EtOAc)], then triturated with ether, to give the product (1.1 g, 62%) as a pale yellow solid; δ_H (CDCl₃, 400 MHz) 3.28 (2H, t), 3.41 (2H, t), 6.78 (1H, d), 6.84 (1H, d), 6.92 (1H, s), 7.20 (1H, d), 7.58 (1H, d), 8.00 (1H, s), 10.43 (1H, s).

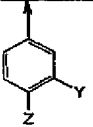
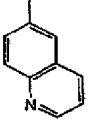
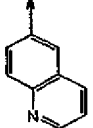
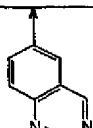
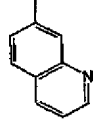
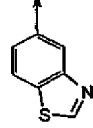
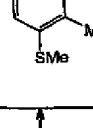
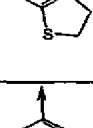
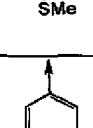

- 5 Compounds of general formula II shown in Table 18 were prepared according to Preparation 19 by reacting the phenol indicated with the required 2-fluorobenzaldehyde. In most cases the crude reaction product after aqueous work-up was used directly in subsequent steps without further purification.

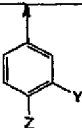
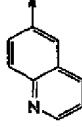


10

Table 18

Preparation	Precursor Phenol	R ⁴	R ⁵		data
20	Prep 3	H	Br		δ_H (CDCl ₃ , 300 MHz) 2.48 (3H, s), 6.81 (3H, m), 7.37 (1H, t), 7.64 (1H, d), 8.06 (1H, s), 10.39 (1H, s); MS <i>m/z</i> (TS ⁺) 358, 360 (MNH ₄ ⁺)
21	Prep 5	H	Br		δ_H (CDCl ₃ , 400 MHz) 3.13 (2H, m), 4.42 (2H, m), 6.55 (1H, s), 6.59 (1H, d), 6.81 (1H, d), 7.04 (1H, d), 7.59 (1H, d), 8.01 (1H, s), 10.40 (1H, s)
22	Prep 2	H	Br		δ_H (CDCl ₃ , 400 MHz) 2.43 (3H, s), 6.78 (1H, d), 6.94 (1H, d), 7.08 (1H, s), 7.19 (1H, d), 7.59 (1H, d), 8.00 (1H, s)
23	commercial	H	Br		δ_H (CDCl ₃ , 300 MHz) 2.35 (3H, s), 2.49 (3H, s), 6.78 (1H, d), 6.90 (2H, s), 7.22 (1H, d), 7.59 (1H, d), 8.05 (1H, s), 10.45 (1H, s); MS <i>m/z</i> (TS ⁺) 356, 354 (MNH ₄ ⁺)
24	commercial	H	MeO		δ_H (CDCl ₃ , 300 MHz) 2.35 (3H, s), 2.45 (3H, s), 3.87 (3H, s), 6.82 (1H, d), 6.83 (1H, s), 6.92 (1H, d), 7.13 (1H, dd), 7.19 (1H, d), 7.40 (1H, d), 10.40 (1H, s); MS <i>m/z</i> (TS ⁺) 389 (MH ⁺)

Preparation	Precursor Phenol	R ⁴	R ⁵		data
25	commercial	H	F		δ_H (CDCl ₃ , 300 MHz) 7.02 (1H, dd), 7.21 (1H, s), 7.30 (1H, m), 7.40 (1H, m), 7.54 (1H, d), 7.66 (1H, dd), 8.01 (1H, d), 8.18 (1H, d), 8.88 (1H, d), 10.43 (1H, s); MS <i>m/z</i> (ES ⁺) 268 (MH ⁺)
26	commercial	H	H		δ_H (CDCl ₃ , 400 MHz) 6.97 (1H, d), 7.21-7.27 (2H, m), 7.38 (1H, dd), 7.49-7.58 (2H, m), 7.92-8.01 (2H, m), 8.11 (1H, d), 8.83 (1H, d), 10.50 (1H, s); MS <i>m/z</i> (ES ⁺) 272 (MNa ⁺), (ES ⁻) 248 (M-H ⁺)
27	<i>J. Chem. Soc.</i> 1952, 4985-4993	H	H		δ_H (CDCl ₃ , 300 MHz) 7.08 (1H, d), 7.36 (2H, m), 7.65 (1H, m), 7.79 (1H, dd), 8.01 (1H, d), 8.13 (1H, d), 9.29 (1H, d), 10.45 (1H, s); MS <i>m/z</i> (TS ⁺) 251 (MH ⁺)
28	commercial	H	H		δ_H (CDCl ₃ , 400 MHz) 7.09 (1H, d), 7.28 (1H, m), 7.35 (1H, m), 7.40 (1H, m), 7.50 (1H, br), 7.59 (1H, m), 7.86 (1H, dd), 7.99 (1H, dt), 8.15 (1H, d), 8.86 (1H, m), 10.46 (1H, s); MS <i>m/z</i> 250 (MH ⁺)
29	<i>Chem. Pharm. Bull.</i> , 1978, 26, 1443	H	H		δ_H (CDCl ₃ , 400 MHz) 6.91 (1H, d), 7.25 (2H, m), 7.55 (2H, m), 7.96 (1H, m), 8.12 (1H, d), 8.95 (1H, s), 10.5 (1H, s); MS <i>m/z</i> 256 (MH ⁺)
30	commercial	H	H		δ_H (CDCl ₃ , 300 MHz) 2.35 (3H, s), 3.44 (3H, s), 6.87 (3H, m), 7.17 (2H, m), 7.50 (1H, t), 7.92 (1H, dd), 10.52 (1H, s); MS <i>m/z</i> (TS ⁺) 259 (MH ⁺)
31	<i>Synth. Commun.</i> 1991, 21, 959-964	H	H		δ_H (CDCl ₃ , 400 MHz) 3.26 (2H, t), 3.39 (2H, m), 6.85 (2H, t), 6.92 (1H, s), 7.18 (2H, m), 7.48 (1H, t), 7.92 (1H, d), 10.51 (1H, s); MS <i>m/z</i> (TS ⁺) 257 (MH ⁺)
32	commercial	Br	H		δ_H (CDCl ₃ , 400 MHz) 2.36 (3H, s), 2.44 (3H, s), 6.88 (2H, m), 6.96 (1H, s), 7.18-7.25 (2H, obs), 7.77 (1H, d), 10.43 (1H, s)
33	Prep 7	H	Br		δ_H (CDCl ₃ , 400 MHz) 3.27 (2H, m), 3.42 (2H, m), 6.67 (1H, d), 6.80 (1H, d), 6.90 (1H, s), 7.16 (1H, d), 7.58 (1H, d), 8.01 (1H, s), 10.41 (1H, s); MS <i>m/z</i> (TS ⁺) 354 (MNH ₄ ⁺)

Preparation	Precursor Phenol	R ⁴	R ⁵		data
34 ^a	commercial	H	CN		δ_H (DMSO-d ₆ , 300 MHz) 6.26 (1H, d), 6.43 (1H, d), 7.49 (1H, d), 7.65-7.71 (2H, m), 7.88 (1H, d), 8.07 (1H, d), 8.17 (1H, s), 8.73 (1H, d), 8.89 (1H, s); MS <i>m/z</i> (ES-) 273 (M-H), (ES ⁺) 275 (MH ⁺)

^a - 4-Fluoro-3-formylbenzonitrile was synthesised according to *Synth. Commun.* 1997, 27(7), 1199 and *J. Org. Chem.* 1961, 26, 2522.

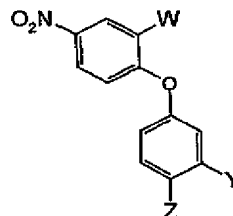
The product from Preparation 30 was also prepared as follows.

5

Potassium carbonate (334.1 g, 2.42 mol) and 4-(methylthio)-m-cresol (273.4 g, 1.77 mol) were added successively to DMF (2 L). 2-Fluorobenzaldehyde (200 g, 1.61 mol) was then added to the slurry and the mixture heated in the range 100-110 °C. After 48 h the reaction mixture was allowed to cool to room temperature and water (1.2 L) added.

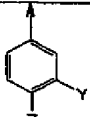
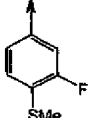

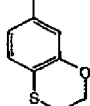
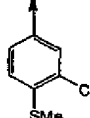

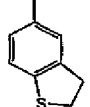

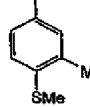

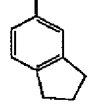
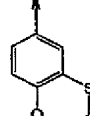
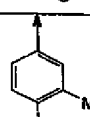
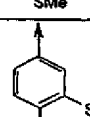
- 10 The solution was cooled to below 10 °C and the pH adjusted to 5 with concentrated HCl (0.37 L), keeping the temperature below 10 °C. Water (0.15 L) and dichloromethane (0.9 L) were added and the mixture stirred. The layers were separated and the organic layer was washed with water (4 x 0.75 L). The solvent was distilled to azeotropically remove the water. Fresh dichloromethane was added as required.
- 15 dichloromethane solution was then concentrated *in vacuo* to give the crude product as an oil (422 g, 100%).

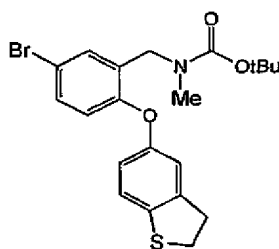
- Compounds of formula IX shown in Table 19 were prepared according to Preparation 19, using either 2-chloro-5-nitrobenzaldehyde or 2-chloro-5-nitrobenzonitrile with the phenol indicated. For these reactions a shorter reaction time (ca. 2-3 h) was usually sufficient to achieve good conversion. In most cases the crude reaction product after aqueous work-up was used directly in subsequent steps without further purification.
- 20



(IX)

Table 19

Preparation	Precursor	W		data
35	Prep 3	-C≡N		δ_H (CDCl ₃ , 400 MHz) 2.48 (3H, s), 6.85-6.95 (3H, m), 7.28 (1H, t), 8.30 (1H, d), 8.52 (1H, s)
36	Prep 5			δ_H (CDCl ₃ , 400 MHz) 3.14 (2H, d), 4.43 (2H, d), 6.62 (2H, m), 6.92 (1H, d), 7.08 (1H, d), 8.27 (1H, d), 8.72 (1H, s), 10.51 (1H, s); MS m/z (TS ⁺) 318 (MH ⁺)
37	Prep 2	-C≡N		δ_H (CDCl ₃ , 300 MHz) 2.55 (3H, s), 6.94 (1H, d), 7.09 (1H, dd), 7.22 (1H, d), 7.27 (1H, d), 8.36 (1H, dd), 8.60 (1H, d); MS m/z (TS ⁺) 338 (MNH ₄ ⁺)
38	Synth. Commun. 1991, 21, 959-964			δ_H (CDCl ₃ , 400 MHz) 3.29 (2H, m), 3.42 (2H, m), 6.88 (2H, m), 6.96 (1H, s), 7.23 (1H, d), 8.26 (1H, d), 8.75 (1H, s), 10.54 (1H, s)
39	commercial			δ_H (CDCl ₃ , 400 MHz) 2.38 (3H, s), 2.50 (3H, s), 6.92 (1H, d), 6.99 (2H, m), 7.24 (1H, d), 8.28 (1H, dd), 8.78 (1H, d), 10.57 (1H, s)
40	commercial			δ_H (CDCl ₃ , 400 MHz) 2.18 (2H, m), 2.95 (4H, t), 6.90 (2H, m), 7.29 (1H, d), 8.27 (1H, d), 8.79 (1H, s), 10.59 (1H, s); MS m/z (TS ⁺) 301 (MNH ₄ ⁺)
41	Prep 4	-C≡N		δ_H (CDCl ₃ , 400 MHz) 3.18 (2H, t), 4.44 (2H, t), 6.76 (1H, d), 6.86 (1H, s), 6.92 (2H, d), 8.32 (1H, d), 8.57 (1H, s); MS m/z (TS ⁺) 332 (MNH ₄ ⁺)
42	commercial	-C≡N		δ_H (CDCl ₃ , 400 MHz) 2.32 (3H, s), 2.47 (3H, s), 6.87 (1H, d), 6.94 (2H, m), 7.21 (1H, d), 8.26 (1H, dd), 8.51 (1H, d); MS m/z (TS ⁺) 318 (MNH ₄ ⁺)
43	Tetrahedron 1982, 38, 2721 & Synthesis 1982, 475	-C≡N		δ_H (CDCl ₃ , 400 MHz) 2.31 (3H, s), 2.41 (3H, s), 6.76 (1H, dd), 6.85 (2H, m), 7.19 (1H, d), 8.24 (1H, dd), 8.53 (1H, d); MS m/z (TS ⁺) 318 (MNH ₄ ⁺)

PREPARATION 44**tert-Butyl 5-bromo-2-(2,3-dihydro-1-benzothien-5-yloxy)benzyl(methyl)carbamate**

The hydrochloride salt of Example 36 (1.04 g, 2.7 mmol) was slurried in DCM (12 mL) and Et₃N (750 μ L, 5.38 mmol) was added, followed by di-*tert*-butyl dicarbonate (766 mg, 3.51 mmol). After stirring at room temperature for 20 min the reaction was quenched by the addition of 0.2M HCl (20 mL). The well shaken mixture was separated and the aqueous layer was extracted with DCM (10 mL). The combined organic layers were dried (MgSO₄) and evaporated to give the product (assumed quantitative yield) as a colourless oil which was used without further purification; δ_H (CDCl₃, 400 MHz) 1.56 (9H, s), 2.82-2.98 (3H, brd), 3.23 (2H, t), 3.40 (2H, t), 4.44 (2H, brd), 6.71 (2H, d), 6.79 (1H, s), 7.12 (1H, d), 7.29 (1H, d), 7.39 (1H, s).

Compounds of formula X shown in Table-20 were prepared according to Preparation 44 starting from the precursors indicated.

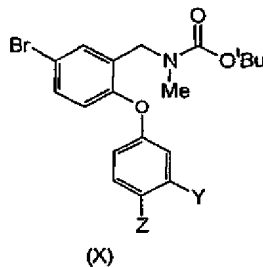
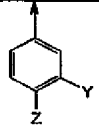
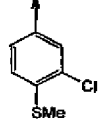

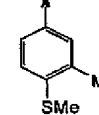


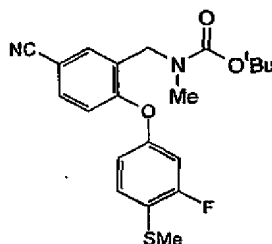
Table 20

Preparation	Precursor		data
45	Example 38		δ_H (CDCl ₃ , 400 MHz) 1.41 (9H, brs), 2.81 (3H, m), 3.07 (2H, m), 4.36 (4H, m), 6.38 (1H, s), 6.43 (1H, d), 6.71 (1H, d), 6.92 (1H, d), 7.26 (1H, d), 7.34 (1H, s); MS <i>m/z</i> (ES ⁺) 468 (MH ⁺)

Preparation	Precursor		data
46	Example 39		δ_H (CDCl ₃ , 400 MHz) 1.48 (9H, s), 2.41 (3H, s), 2.82 (3H, brd), 4.39 (2H, brd), 6.73 (1H, d), 6.80 (1H, d), 6.93 (1H, s), 7.04 (1H, d), 7.32 (1H, d), 7.39 (1H, s); MS m/z (TS ⁺) 474 (MH ⁺)
47	Example 37		δ_H (CDCl ₃ , 300 MHz) 1.46 (9H, brs), 2.46 (3H, s), 2.89 (3H, brs), 4.41 (2H, brs), 6.68 (2H, m), 6.82 (1H, d), 7.27 (1H, obs), 7.40 (1H, d), 7.43 (1H, s); MS m/z (TS ⁺) 458 (MH ⁺)
48	Example 44		δ_H (CDCl ₃ , 300 MHz) 1.45 (9H, br) 2.38 (3H, s), 2.44 (3H, s), 2.90 (3H, br), 4.47 (2H, br), 6.70-6.81 (3H, m) 7.20 (1H, d), 7.24-7.58 (2H, m)

PREPARATION 49

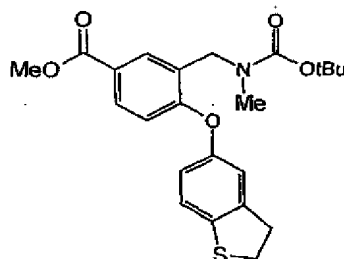
tert-Butyl 5-cyano-2-[3-fluoro-4-(methylsulfanyl)phenoxy]benzyl-(methyl)carbamate



- 5 The title compound was prepared from the bromide of Preparation 47 by the method of Example 78; δ_H (CDCl₃, 300 MHz) 1.48 (9H, brs), 2.50 (3H, s), 2.93 (3H, brs), 4.55 (2H, brs), 6.79 (2H, m), 6.88 (1H, d), 7.35 (1H, t), 7.53 (1H, d), 7.59 (1H, s); MS m/z (TS⁺) 403 (MH⁺).

10 PREPARATION 50

Methyl 3-[[[(tert-butoxycarbonyl)(methyl)amino]methyl]-4-(2,3-dihydro-1-benzothien-5-yloxy)benzoate



- A mixture of the bromide of Preparation 44 (1.22 g, 2.7 mmol), Et₃N (1.13 mL, 8.11 mmol) and dichlorobis(triphenylphosphine)palladium (II) (190 mg, 0.27 mmol) in MeOH

(14 mL) was heated at 80°C under 100 psi pressure of CO for 18 h. Analysis by tlc indicated the reaction was not complete so a further portion of catalyst (190 mg, 0.27 mmol) was added and the mixture was heated at 100°C under 100 psi pressure of CO for 24 h. The mixture was diluted with EtOAc (20 mL) and filtered through a pad of silica gel, eluting with excess EtOAc. The solvent was removed *in vacuo* and the residue was partitioned between EtOAc (50 mL) and a 2:1 mixture of water:880 NH₃ (50 mL). The aqueous layer was extracted with EtOAc (25 mL) and the combined organic layers were dried (MgSO₄) and evaporated. Purification by column chromatography [SiO₂; 4:1 (pentane/EtOAc)] gave the product (970 mg, 84%) as an oil; δ_H (CDCl₃, 400 MHz) 1.42 (9H, s), 2.90 (3H, brs), 3.22 (2H, t), 3.38 (2H, t), 3.84 (3H, s), 4.50 (2H, brd), 6.74 (2H, d), 6.82 (1H, s), 7.13 (1H, d), 7.82 (1H, d), 7.93 (1H, brd); MS *m/z* (ES⁺) 430 (MH⁺).

Compounds of formula XI shown in Table 21 were prepared according to Preparation 50 starting from the precursors indicated.

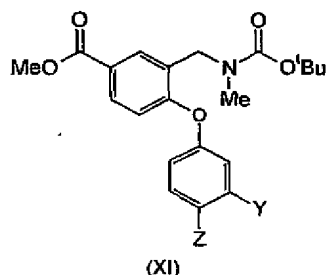
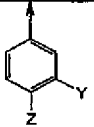
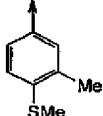


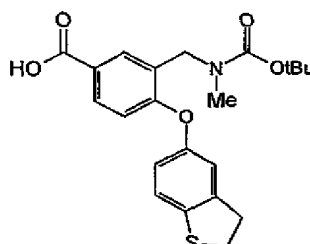
Table 21

Preparation	Precursor		data
51	Prep 45		δ_H (CDCl ₃ , 400 MHz) 1.42 (9H, s), 2.86 (2H, m), 3.07 (2H, m), 3.85 (3H, s), 4.37 (2H, m), 4.48 (2H, m), 6.48 (2H, m), 6.79 (1H, d), 6.97 (1H, d), 7.83 (1H, d), 7.95 (1H, s); MS <i>m/z</i> (ES ⁺) 446 (MH ⁺)
52	Prep 46		δ_H (CDCl ₃ , 400 MHz) 1.43 (9H, brs), 2.47 (3H, s), 2.88 (3H, brd), 3.90 (3H, s), 4.51 (2H, brd), 6.81 (1H, d), 6.91 (1H, d), 7.06 (1H, s), 7.20 (1H, d), 7.89 (1H, d), 7.98 (1H, brd); MS <i>m/z</i> (TS ⁺) 469 (MNH ₄ ⁺)
53	Prep 47		δ_H (CDCl ₃ , 300 MHz) 1.47 (9H, brs), 2.46 (3H, s), 2.91 (3H, brs), 3.94 (3H, s), 4.52 (2H, brs), 6.78 (2H, m), 6.91 (1H, d), 7.35 (1H, m), 7.92 (1H, d), 8.02 (1H, brs); MS <i>m/z</i> (TS ⁺) 453 (MNH ₄ ⁺)

Preparation	Precursor		data
54	Prep 48		δ_H (CDCl ₃ , 300 MHz) 1.44 (9H, s), 2.37 (3H, s), 2.47 (3H, s), 2.94 (3H, br), 3.90 (3H, s), 4.73 (2H, br), 6.79-6.87 (3H, m), 7.20 (1H, d), 7.86 (1H, d), 8.00 (1H, br); MS m/z (ES ⁺) 454 (MNa ⁺)

PREPARATION 55

3-(((tert-Butoxycarbonyl)(methyl)amino)methyl)-4-(2,3-dihydro-1-benzothien-5-yloxy)benzoic acid

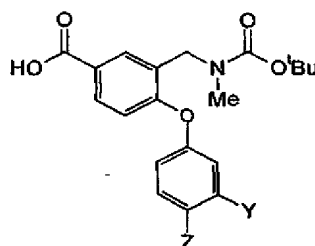


5

A solution of the ester of Preparation 50 (970 mg, 2.26 mmol) in THF (20 mL) and 1M LiOH (20 mL) was heated at reflux for 16 h. After cooling to room temperature the THF was removed *in vacuo*, the residue was neutralised with sat aq NH₄Cl and the mixture was extracted with DCM (100 mL) and then ether (100 mL). The combined organic

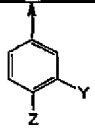
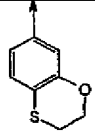
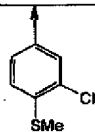
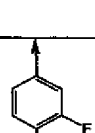
10 layers were dried (MgSO₄) and evaporated to give a white foam (960 mg) which was used without further purification; δ_H (CDCl₃, 400 MHz) 1.30 (9H, s), 2.78 (3H, brs), 3.20 (2H, brs), 3.38 (2H, t), 4.41 (2H, m), 6.62 (2H, m), 6.78 (1H, m), 7.10 (1H, m), 7.84 (1H, m), 7.99 (1H, m); MS m/z (ES⁻) 414 (M-H).

15 Compounds of formula XII shown in Table 22 were prepared according to Preparation 55 from the precursors indicated.



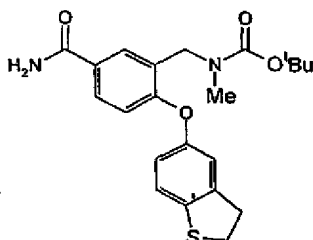
(XII)

Table 22

Preparation	Precursor		data
56	Prep 51		δ_H (CDCl ₃ , 400 MHz) 1.26 (9H, s), 2.74 (3H, s), 3.02 (2H, m), 4.31 (4H, m), 6.38 (2H, m), 6.64 (1H, d), 6.87 (1H, d), 7.68 (1H, brs), 7.78 (1H, brs); MS m/z (ES ⁻) 430 (M-H ⁺)
57	Prep 52		δ_H (CDCl ₃ , 400 MHz) 1.44 (9H, brs), 2.49 (3H, s), 2.92 (3H, brd), 4.57 (2H, brd), 6.82 (1H, d), 6.94 (1H, d), 7.08 (1H, s), 7.21 (1H, d), 7.97 (1H, d), 8.04 (1H, brd); MS m/z (ES ⁻) 436 (M-H ⁺)
58	Prep 53		δ_H (CDCl ₃ , 300 MHz) 1.46 (9H, brs), 2.49 (3H, s), 2.93 (3H, brs), 4.57 (2H, brs), 6.77 (2H, m), 6.92 (1H, d), 7.32 (1H, t), 7.99 (1H, d), 8.08 (1H, brs); MS m/z (ES ⁻) 420 (M-H ⁺)

PREPARATION 59

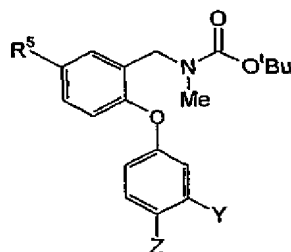
tert-Butyl 5-(aminocarbonyl)-2-(2,3-dihydro-1-benzothien-5-yloxy)benzyl-
 5 (methyl)carbamate



Et₃N (267 μ L, 1.92 mmol), HOBt.H₂O (129 mg, 0.84 mmol) and WSCDI (191 mg, 1.0 mmol) were added to a solution of the acid of Preparation 55 (318 mg, 0.77 mmol) in DCM (10 mL) and the mixture was stirred for 1 h before the addition of a saturated solution of NH₃ in THF (2 mL). After stirring for a further 16 h the reaction was diluted with water (50 mL), 0.2M HCl (20 mL) and DCM (25 mL). The organic layer was separated and the aqueous layer was extracted with DCM (25 mL). The combined organic layers were dried (MgSO₄) and evaporated to give a white foam (assumed quantitative yield) which was used without further purification; δ_H (CDCl₃, 400 MHz) 1.44 (9H, s), 2.91 (3H, br), 3.27 (2H, t), 3.40 (2H, t), 4.54 (2H, br), 6.75-6.88 (3H, m), 7.18 (1H, d), 7.68 (1H, d), 7.74 (1H, s).

Compounds of formula XIII shown in Table 23 were prepared according to Preparation 59 from the precursors indicated.

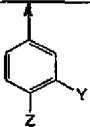
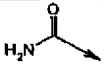
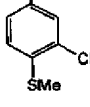
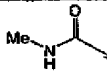
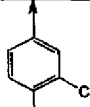
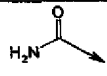
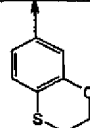
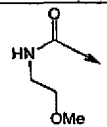
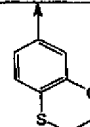
80



(XIII)

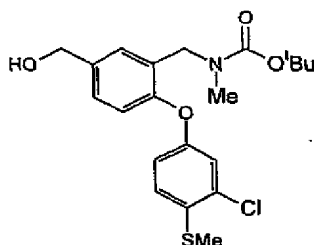
Table 23

Preparation	Precursor	R ⁵		data
60	Prep 55			δ_H (CDCl ₃ , 400 MHz) 1.43 (9H, s), 2.83-3.00 (6H, m), 3.24 (2H, t), 3.39 (2H, t), 4.51 (2H, brs), 6.70-6.85 (3H, m), 7.15 (1H, d), 7.62 (1H, d), 7.68 (1H, s)
61	Prep 55			δ_H (CDCl ₃ , 400 MHz) 1.46 (9H, s), 2.89 (3H, br), 3.24 (2H, t), 3.37-3.43 (5H, m), 3.56 (2H, t), 3.63 (2H, m), 4.54 (2H, br), 6.46 (1H, br), 6.75-6.86 (3H, m), 7.16 (1H, d), 7.62 (1H, d), 7.69 (1H, s)
62	Prep 58			δ_H (d ₆ -DMSO, 400 MHz) 1.29 (9H, br), 2.40 (3H, s), 2.75 (3H, s), 4.39 (2H, s), 6.78 (1H, d), 6.91 (2H, m), 7.23 (1H, br), 7.36 (1H, t), 7.78 (2H, m), 7.90 (1H, br); MS m/z (TS ⁺) 438 (MNH ₄ ⁺)
63	Prep 58			δ_H (CDCl ₃ , 400 MHz) 1.41 (9H, s), 2.40 (3H, s), 2.92 (3H, brs), 2.98 (3H, d), 4.45 (2H, brs), 6.10 (1H, brs), 6.67 (2H, m), 6.88 (1H, d), 7.27 (1H, obs), 7.63 (2H, m); MS m/z (TS ⁺) 452 (MNH ₄ ⁺)
64	Prep 58			δ_H (CDCl ₃ , 400 MHz) 1.40 (9H, s), 2.40 (3H, s), 2.81 (3H, brs), 3.35 (3H, s), 3.53 (2H, m), 3.61 (2H, m), 4.44 (2H, brs), 6.45 (1H, brs), 6.66 (2H, m), 6.87 (1H, d), 7.29 (1H, d), 7.64 (1H, d), 7.72 (1H, s); MS m/z (TS ⁺) 479 (MH ⁺)

Preparation	Precursor	R ⁵		data
65	Prep 57			δ_H (CDCl ₃ , 400 MHz) 1.43 (9H, brs), 2.47 (3H, s), 2.90 (3H, brd), 4.52 (2H, brs), 6.87 (1H, d), 6.91 (1H, d), 7.03 (1H, s), 7.10 (1H, d), 7.72 (1H, d), 7.78 (1H, s); MS m/z (ES ⁺) 435 (M-H ⁺)
66	Prep 57			δ_H (CDCl ₃ , 400 MHz) 1.42 (9H, brs), 2.47 (3H, s), 2.88 (3H, brd), 3.00 (3H, d), 4.48 (2H, brs), 6.16 (1H, brd), 6.85 (2H, m), 7.01 (1H, s), 7.19 (1H, d), 7.67 (2H, m); MS m/z (ES ⁺) 449 (M-H ⁺)
67	Prep 56			δ_H (CDCl ₃ , 400 MHz) 1.42 (9H, s), 2.86 (3H, m), 3.08 (2H, m), 3.97 (2H, m), 4.48 (2H, brs), 5.86-6.27 (2H, brs), 6.45 (1H, s), 6.49 (1H, d), 6.82 (1H, d), 6.96 (1H, d), 7.64 (1H, d), 7.71 (1H, s); MS m/z (TS ⁺) 331 (MH ⁺ -Boc)
68	Prep 56			δ_H (CDCl ₃ , 400 MHz) 1.26 (9H, s), 2.74 (3H, s), 3.02 (2H, m), 4.31 (4H, m), 6.38 (2H, m), 6.64 (1H, d), 6.87 (1H, d), 7.68 (1H, brs), 7.78 (1H, brs); MS m/z (ES ⁺) 430 (M-H ⁺)

PREPARATION 69

tert-Butyl 2-[3-chloro-4-(methylsulfanyl)phenoxy]-5-(hydroxymethyl)benzyl-(methyl)carbamate



5

A solution of LiAlH₄ in THF (1M, 2 mL, 2 mmol) was added dropwise to a solution of the ester of Preparation 52 (452 mg, 1 mmol) in THF (10 mL) under N₂. Once the reaction was judged complete by tlc analysis, ether (10 mL) was added and the excess LiAlH₄ was quenched by the cautious addition of 2M NaOH. The organic layer was separated, washed with brine, dried (MgSO₄) and evaporated. Purification of the residue by column chromatography [SiO₂; 39:1 (DCM/MeOH)] gave the desired alcohol (200 mg, 47%) as a

10

gummy white solid; δ_H (CDCl₃, 400 MHz) 1.41 (9H, brs), 1.80 (1H, brs), 2.43 (3H, s), 2.81 (3H, brd), 4.42 (2H, brd), 4.66 (2H, s), 6.82 (1H, d), 6.88 (1H, d), 6.96 (1H, s), 7.16 (1H, d), 7.27 (2H, obs); MS m/z (ES⁺) 446 (MNa⁺).

- 5 Compounds of formula XIV shown in Table 24 were prepared according to Preparation 69 starting from the precursors indicated.

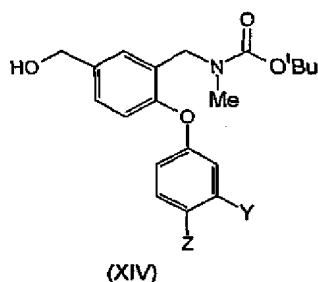
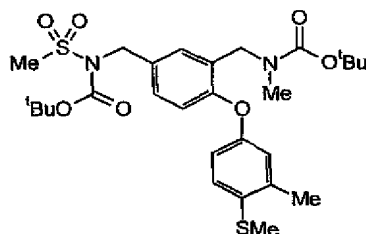


Table 24

Preparation	Precursor		data
70	Prep 53		δ_H (CDCl ₃ , 400 MHz) 1.39 (9H, brs), 1.99 (1H, brs), 2.39 (3H, s), 2.78 (3H, brd), 4.39 (2H, brs), 4.62 (2H, d), 6.61 (2H, t), 6.88 (1H, d), 7.20-7.30 (3H, m+CHCl ₃); MS m/z (TS ⁺) 408 (MH ⁺)
71	Prep 54		δ_H (CDCl ₃ , 300 MHz) 1.45 (9H, s), 2.34 (3H, s), 2.46 (3H, s), 2.90 (3H, br), 4.49 (2H, s), 4.67 (2H, s), 6.72-6.81 (2H, m), 6.85 (1H, d), 7.18 (1H, d), 7.21-7.30 (2H, obs); MS m/z (TS ⁺) 404 (MH ⁺)

PREPARATION 72

tert-Butyl 3-[(*tert*-butoxycarbonyl)(methyl)amino]methyl-4-[3-methyl-4-(methylsulfanyl)phenoxy]benzyl(methylsulfonyl)carbamate



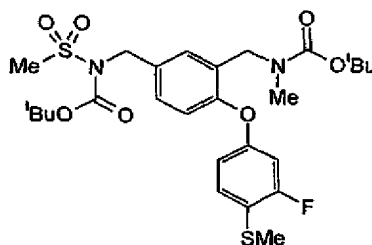
15

A solution of diethyl azodicarboxylate (505 μ L, 3.21 mmol) in THF (5 mL) was added dropwise to a solution of *tert*-butyl methylsulfonylcarbamate (synthesised according to

Tetrahedron Lett. 1994, 35, 379-380) (655 mg, 3.36 mmol), the alcohol of Preparation 71 (1.226 g, 3.04 mmol) and triphenylphosphine (880 mg, 3.36 mmol) in THF (15 mL) at 0°C. The reaction was stirred at 0°C for 2 h then diluted with EtOAc (80 mL) and washed with 10% aq. K₂CO₃ (100 mL). The organic layer was washed with brine, dried (MgSO₄) and evaporated. The residue was purified by column chromatography [SiO₂; 1:4 EtOAc:pentane] to give the title compound (1.406 g, 80%) as a colourless oil; δ_H (CDCl₃, 300 MHz) 1.45 (9H, s), 1.52 (9H, s), 2.38 (3H, s), 2.44 (3H, s), 2.83 (3H, s), 3.22 (3H, s), 4.49 (2H, s), 4.85 (2H, s), 6.74-6.83 (3H, m), 7.18-7.29 (3H, obs); MS *m/z* (TS⁺) 481 (MH⁺-BOC).

PREPARATION 73

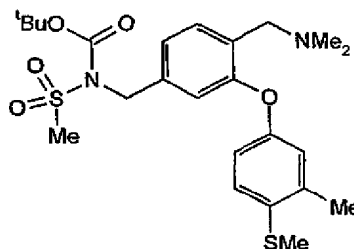
tert-Butyl 3-[[*tert*-butoxycarbonyl](methyl)amino]methyl]-4-[3-fluoro-4-(methylsulfanyl)phenoxy]benzyl(methylsulfonyl)carbamate



The title compound was prepared from the alcohol of Preparation 70 by the method of Preparation 72; δ_H (CDCl₃, 300 MHz) 1.44 (9H, s), 1.52 (9H, s), 2.44 (3H, s), 2.82 (3H, s), 3.23 (3H, s), 4.45 (2H, s), 4.87 (2H, s), 6.61-6.70 (2H, m), 6.90 (1H, d), 7.25-7.33 (3H, m); MS *m/z* (ES⁺) 607 (MNa⁺).

PREPARATION 74

tert-Butyl 4-[(dimethylamino)methyl]-3-[3-methyl-4-(methylsulfanyl)phenoxy]benzyl(methylsulfonyl)carbamate

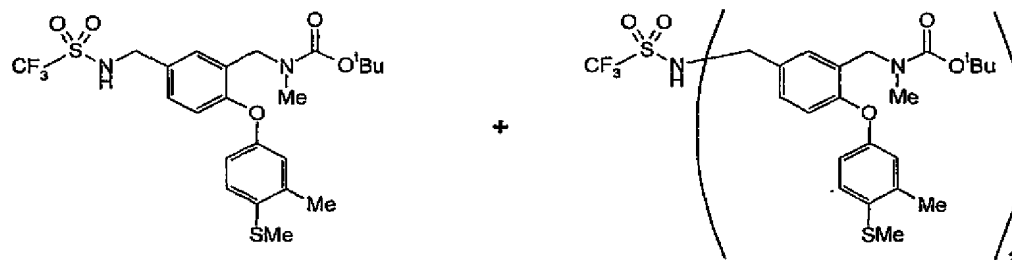


The title compound was prepared from the alcohol of Example 59 by the method of Preparation 72. The crude product was not purified by column chromatography but taken on directly to the next step; δ_H (CDCl₃, 400 MHz) 1.39 (9H, s), 2.22 (6H, s), 2.28 (3H, s),

2.38 (3H, s), 3.07 (3H, s), 3.42 (2H, s), 4.76 (2H, s), 6.72 (2H, m), 6.79 1H, s), 7.07 (1H, d), 7.12 (1H, d), 7.40 (1H, obs).

PREPARATION 75

- 5 *tert*-Butyl methyl[2-[3-methyl-4-(methylsulfonyl)phenoxy]-5-(((trifluoromethyl)sulfonyl)amino)methyl)benzyl]carbamate



The title compound was prepared from the alcohol of Preparation 71 by the method of Preparation 72 using trifluoromethanesulfonamide instead of *tert*-butyl

- 10 methylsulfonylcarbamate. The desired product was contaminated with *tert*-butyl 5-({3-[[*tert*-butoxycarbonyl(methyl)amino]methyl]-4-[3-methyl-4-(methylsulfonyl)phenoxy]benzyl}[(trifluoromethyl)sulfonyl]amino)methyl)-2-[3-methyl-4-(methylsulfonyl)phenoxy]benzyl(methyl)carbamate and was taken on as a mixture; MS m/z (ES⁻) 533 (M-H⁺).

15

Compounds of formula XV shown in Table 25 were prepared according to Preparation 44 using the precursors indicated.

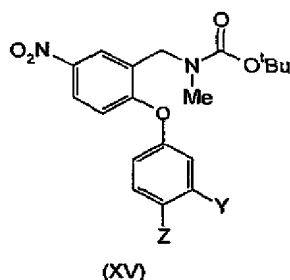
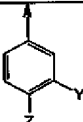
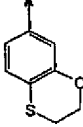
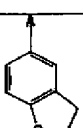
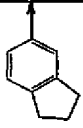
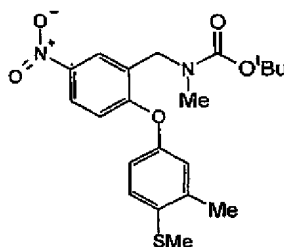


Table 25

Preparation	Precursor		data
76	Example 41		δ_H (CDCl ₃ , 400 MHz) (major rotamer) 1.51 (9H, s), 2.92 (3H, s), 3.10 (2H, m), 4.40 (2H, m), 4.52 (2H, br), 6.53 (2H, m), 6.81 (1H, m), 7.03 (1H, d), 7.97-8.21 (2H, m); MS m/z (TS ⁺) 433 (MH ⁺)
77	Example 40		δ_H (CDCl ₃ , 300 MHz) 1.50 (9H, br), 2.99 (3H, s), 3.29 (2H, m), 3.43 (2H, m), 4.60 (2H, br), 6.81 (2H, m), 6.91 (1H, s), 7.22 (1H, d), 8.04 (1H, d), 8.21 (1H, br)
78	Example 42		δ_H (CDCl ₃ , 400 MHz) 1.56 (9H, s), 2.15 (2H, m), 2.85-3.00 (7H, m), 4.60 (2H, brd), 6.78 (2H, m), 6.87 (1H, s), 7.12 (1H, d), 8.03 (1H, d), 8.10 (1H, s); MS m/z (TS ⁺) 399 (MH ⁺)

PREPARATION 79

tert-Butyl methyl{2-[3-methyl-4-(methylsulfanyl)phenoxy]-5-nitrobenzyl}carbamate



5

N-Methyl-*N*-(2-[3-methyl-4-(methylsulfanyl)phenoxy]-5-nitrobenzyl)amine and {2-[3-methyl-4-(methylsulfanyl)phenoxy]-5-nitrophenyl}methanol.

To a suspension of the aldehyde of Preparation 39 (21.0 g, 69.2 mmol) in EtOH (100 mL) was added 8M methylamine in EtOH (86.5 ml, 692 mmol). A solution was given and after stirring for a short time a precipitate was observed. This was re-dissolved by the addition of THF (100 mL), the solution was cooled to 0°C and NaBH₄ (7.85 g, 208 mmol) was then added. The reaction was allowed to warm slowly to room temperature and stirred overnight before the solvent was removed *in vacuo*. The residue was taken up in water (150 mL) and ether (150 mL), and 2M HCl was added cautiously until pH 1. The layers were separated and the aqueous layer was washed with ether (2×100 mL). The combined organic extracts were dried and evaporated to give {2-[3-methyl-4-(methylsulfanyl)phenoxy]-5-nitrophenyl}methanol (18.9 g, 89%) as a yellow solid; δ_H

(CDCl₃, 400 MHz) 2.35 (3H, s), 2.48 (3H, s), 4.90 (2H, s), 6.79 (1H, d), 6.89 (1H, s), 6.91 (1H, d), 7.22 (1H, d), 8.07 (1H, dd), 8.41 (1H, d).

The aqueous layer from above was neutralised by pouring onto excess solid K₂CO₃. The basic solution was extracted with ether (2×100 mL) and these ether extracts were dried
5 (MgSO₄) and evaporated to give *N*-methyl-*N*-{2-[3-methyl-4-(methylsulfanyl)phenoxy]-5-nitrobenzyl}amine (1.65 g, 7.5%) as an orange oil; MS *m/z* (ES⁺) 319 (MH⁺).

N-Methyl-*N*-{2-[3-methyl-4-(methylsulfanyl)phenoxy]-5-nitrobenzyl}amine from {2-[3-methyl-4-(methylsulfanyl)phenoxy]-5-nitrophenyl}methanol.

Methanesulfonyl chloride (4.81 mL, 61.9 mmol) was added slowly to a solution of {2-[3-methyl-4-(methylsulfanyl)phenoxy]-5-nitrophenyl}methanol (18.9 g, 61.9 mmol) and Et₃N
10 (9.5 mL, 68.2 mmol) in DCM (60 mL). The mixture was stirred at room temperature for 3 h then poured into water and extracted with DCM (3 times). The combined organic extracts were dried (MgSO₄) and evaporated to give a dark, viscous oil. This oil was taken up in DCM (50 mL) and 8M methylamine in EtOH (200 mL, 1.6 mol) was added
15 followed by Et₃N (10 mL, 71.7 mmol). After stirring for 18 h the mixture was concentrated *in vacuo* to give crude amine which was used without further purification.

tert-Butyl methyl{2-[3-methyl-4-(methylsulfanyl)phenoxy]-5-nitrobenzyl}carbamate

The crude amine from above was dissolved in DCM (100 mL) at 0°C and Et₃N (11.4 mL, 81.8 mmol) was added, followed by di-*tert*-butyl dicarbonate (15.0 g, 68.7 mmol). The
20 reaction was allowed to warm to room temperature and stirred for 16 h before being concentrated *in vacuo*. The residue was partitioned between EtOAc and water and the aqueous layer was extracted with EtOAc (2 times). The combined organic layers were dried (MgSO₄) and evaporated. The residue was purified by column chromatography (SiO₂; 1st column - 3% MeOH in DCM; 2nd column EtOAc:pentane 1:3) to give the title
25 compound (14.2 g, 54%) as a yellow oil; δ_H (CDCl₃, 400 MHz) 1.44 (9H, s), 2.32 (3H, s), 2.44 (3H, s), 2.95 (3H, s), 4.56 (2H, br), 6.75 (1H, d), 6.84 (2H, m), 7.17 (1H, d), 8.00 (1H, d), 8.18 (1H, br); MS *m/z* (TS⁺) 419 (MH⁺).

Compounds of formula XVI shown in Table 26 were prepared according to Example 103
30 from the precursors indicated

87

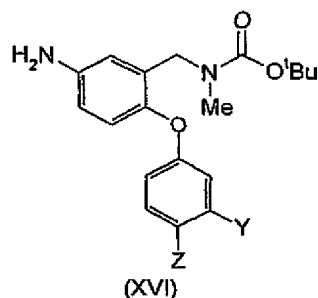
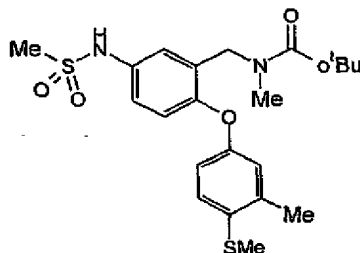


Table 26

Preparation	Precursor		data
80	Prep 77		δ_H (CDCl ₃ , 300 MHz) 1.50 (9H, br), 2.80 (3H, br), 3.20 (2H, m), 2.37 (2H, m), 3.60 (2H, br), 4.40 (2H, s), 6.50-6.80 (5H, m), 7.05 (1H, d); MS m/z (ES ⁺) 387 (MH ⁺)
81	Prep 78		δ_H (CDCl ₃ , 400 MHz) 1.42 (9H, s), 2.05 (2H, m), 2.80 (7H, m), 4.37 (2H, s), 6.50-6.65 (3H, m), 6.69 (1H, s), 6.78 (1H, d), 7.08 (1H, d); MS m/z (TS ⁺) 369 (MH ⁺)
82	Prep 76		δ_H (CDCl ₃ , 400 MHz) 1.43 (9H, s), 2.88 (3H, br), 3.07 (2H, m), 3.59 (2H, br), 4.30 (2H, s), 4.36 (2H, m), 6.32 (1H, s), 6.40 (1H, d), 6.49-6.65 (2H, m), 6.75 (1H, d), 6.88 (1H, d); MS m/z (TS ⁺) 403 (MH ⁺)
83	Prep 79		δ_H (CDCl ₃ , 300 MHz) 1.47 (9H, s), 2.33 (3H, s), 2.40 (3H, s), 2.82 (3H, br), 3.60 (2H, s), 4.35 (2H, s), 6.50-6.77 (4H, m), 6.80 (1H, d), 7.16 (1H, d); MS m/z (TS ⁺) 389 (MH ⁺)

5 PREPARATION 84

tert-Butyl methyl{2-[3-methyl-4-(methylsulfonyl)phenoxy]-5-[(methylsulfonyl)amino]benzyl}carbamate

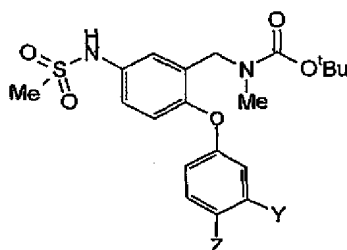


- 10 Methanesulfonyl chloride (4.16 mL, 53.7 mmol) was added dropwise to a solution of the aniline of Preparation 83 (9.5 g, 24.5 mmol) and Et₃N (7.5 mL, 53.8 mmol) in DCM (50 mL) at 0°C. After stirring at 0°C for 30 min the reaction was allowed to warm to room

temperature before the solvent was removed *in vacuo*. 2M NaOH (50 mL) was added to the residue and the mixture was stirred for 30 min. The mixture was extracted with EtOAc and the organic layer was washed with brine, dried (MgSO₄) and evaporated to give an oil. Purification by column chromatography [SiO₂; 97.5:2.5:0.25

- 5 (DCM/MeOH/880 NH₃) gave the product (9.0 g, 79%) as a brown foam; δ_H (CDCl₃, 300 MHz) 1.43 (9H, brs), 2.35 (3H, s), 2.42 (3H, s), 2.88 (3H, brs), 3.01 (3H, s), 4.46 (2H, brs), 6.76 (2H, d+s), 6.83 (1H, d), 7.16 (1H, s), 7.20 (2H, brs); MS *m/z* (ES⁺) 467 (MH⁺).

- 10 Compounds of formula XVII shown in Table 27 were prepared according to Preparation 84 from the precursors indicated.



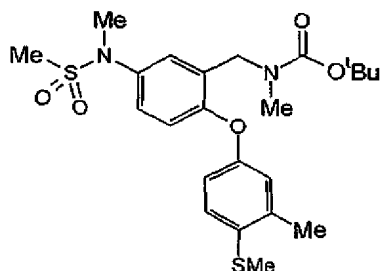
(XVII)

Table 27

Preparation	Precursor		data
85	Prep 81		δ_H (CDCl ₃ , 400 MHz) (rotamers) 1.44 and 1.48 (9H, 2xs), 2.10 (2H, quintet), 2.88 (7H, m), 3.00 (3H, s), 4.49 (2H, br), 6.23 (1H, br), 6.72 (1H, d), 6.81 (1H, s), 6.83 (1H, d), 7.13 (3H, m); MS <i>m/z</i> (TS ⁺) 347 (MH ⁺ -Boc)
86	Prep 80		Product used without purification.
87	Prep 82		δ_H (CDCl ₃ , 400 MHz) (rotamers) 1.40 and 1.44 (9H, 2xs), 2.80 and 2.85 (3H, 2xs), 2.95 (3H, s), 3.07 (2H, m), 4.38 (2H, m), 6.36 (1H, s), 6.44 (1H, d), 6.84 (1H, d), 6.92 (1H, d), 7.12 (2H, m); MS <i>m/z</i> (TS ⁺) 498 (MNH ₄ ⁺)

PREPARATION 88

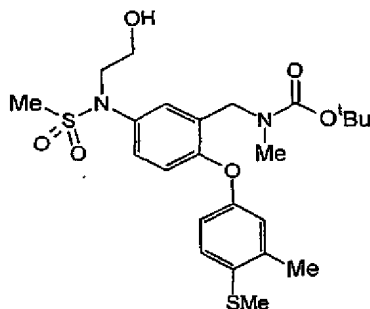
tert-Butyl methyl{2-[3-methyl-4-(methylsulfonyl)phenoxy]-5-[methyl(methylsulfonyl)amino]benzyl}carbamate



- 5 MeI (1.07 mL, 17.2 mmol) was added dropwise to a mixture of the sulfonamide of Preparation 84 (2.0 g, 4.3 mmol) and K_2CO_3 (592 mg, 4.3 mmol) in CH_3CN (10 mL) under N_2 . The mixture was stirred for 16 h and then partitioned between EtOAc (50 mL) and 2M NaOH (50 mL). The organic layer was washed with brine, dried ($MgSO_4$) and evaporated. The residue was purified by column chromatography [SiO_2 ; 590:10:1 (DCM/MeOH/880 NH_3)] to give the product (1.23 g, 60%) as a yellow oil; δ_H ($CDCl_3$, 300 MHz) 1.45 (9H, s), 2.34 (3H, s), 2.42 (3H, s), 2.86 (3H, s), 2.90 (3H, s), 3.28 (3H, s), 4.49 (2H, s), 6.80 (3H, br), 7.18 (3H, m); MS m/z (TS^+) 498 (MNH_4^+).

PREPARATION 89

- 15 *tert*-Butyl 5-[(2-hydroxyethyl)(methylsulfonyl)amino]-2-[3-methyl-4-(methylsulfonyl)phenoxy]benzyl(methyl)carbamate

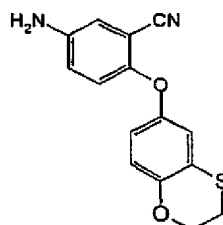


- 2-Bromoethanol (1.34 mL, 18.9 mmol) was added to a mixture of the sulfonamide of Preparation 84 (2.0 g, 4.3 mmol) and K_2CO_3 (2.605 g, 18.8 mmol) in CH_3CN (10 mL) under N_2 . The mixture was heated at reflux for 16 h, cooled and then partitioned between EtOAc (50 mL) and 2M NaOH (50 mL). The organic layer was washed with brine, dried ($MgSO_4$) and evaporated. The residue was purified by column chromatography [SiO_2 ; 390:10:1 (DCM/MeOH/880 NH_3)] to give the product (524 mg, 24%) as a pink foam; δ_H ($CDCl_3$, 300 MHz) 1.42 (9H, s), 2.37 (3H, s), 2.43 (3H, s), 2.91

(3H, s), 2.98 (3H, s), 3.68 (2H, brs), 3.79 (2H, d), 4.49 (2H, s), 6.81 (3H, m), 7.19 (3H, m); MS m/z (TS^+) 528 (MNH_4^+).

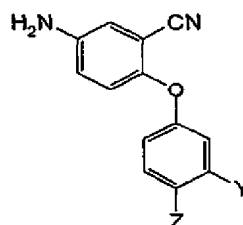
PREPARATION 90

5 5-Amino-2-(2,3-dihydro-1,4-benzoxathin-6-yloxy)benzonitrile



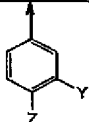
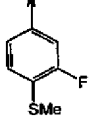
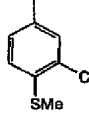
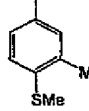
Fe powder (930 mg, 16.7 mmol) was added to the nitro compound of Preparation 41 (740 mg, 2.38 mmol) in AcOH (5 mL) and water (1 mL) and the mixture was stirred at room temperature for 16 h. The solvent was removed *in vacuo*, the residue was taken up in EtOAc (50 mL) and 10% aq K_2CO_3 (50 mL) and filtered through Arbocel®. The organic layer was separated and the aqueous layer was extracted with EtOAc (50 mL). The combined organic extracts were dried ($MgSO_4$) and evaporated to a brown foam (670 mg, 99%) which was used without further purification; δ_H ($CDCl_3$, 400 MHz) 3.18 (2H, m), 4.36 (2H, m), 6.60-6.70 (2H, m), 6.70-6.80 (3H, m), 6.85 (1H, s); MS m/z (TS^+) 302 (MNH_4^+).

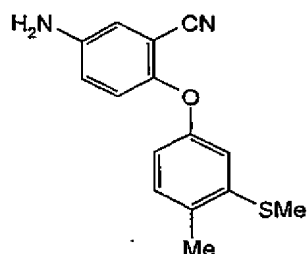
Compounds of formula Vb, i.e. compounds of formula V where T is cyano, R^4 is hydrogen and R^5 is amino, shown in Table 28 were prepared according to Preparation 90 from the precursors indicated.



(Vb)

Table 28

Preparation	Precursor		data
91	Prep 35		δ_H (CDCl ₃ , 400 MHz) 2.40 (3H, s), 6.62-6.72 (2H, m), 6.80-6.90 (3H, m), 7.28 (1H, d)
92	Prep 37		δ_H (CDCl ₃ , 300 MHz) 2.47 (3H, s), 3.83 (2H, br), 6.83-6.94 (4H, m), 7.01 (1H, s), 7.19 (1H, d); MS m/z (TS ⁺) 308 (MNH ₄ ⁺)
93	Prep 42		δ_H (CDCl ₃ , 400 MHz) 2.30 (3H, s), 2.40 (3H, s), 3.84 (2H, br), 6.77 (4H, m), 6.85 (1H, s), 7.13 (3H, d); MS m/z (TS ⁺) 288 (MNH ₄ ⁺)

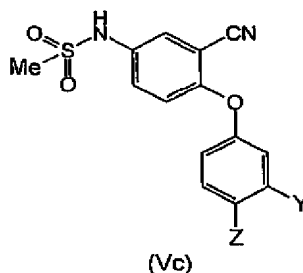
PREPARATION 94**5-Amino-2-[4-methyl-3-(methylsulfonyl)phenoxy]benzonitrile**

5

The title compound was prepared from the nitro compound of Preparation 43 by the method of Example 103; δ_H (CDCl₃, 400 MHz) 2.27 (3H, s), 2.41 (3H, s), 3.66 (2H, br), 6.62 (1H, d), 6.79 (2H, s), 6.82 (1H, s), 6.89 (1H, s), 7.08 (1H, d); MS m/z (ES⁺) 293 (MNa⁺), (ES⁻) 269 (M-H⁺).

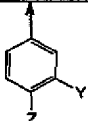
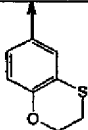
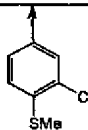
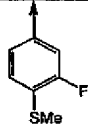
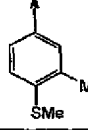
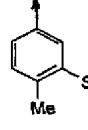
10

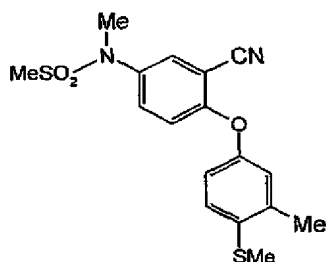
Compounds of formula Vc, i.e. compounds of formula V where T is cyano, R⁴ is hydrogen and R⁵ is -NHSO₂Me, shown in Table 29 were prepared according to Preparation 84 from the precursors indicated.



15

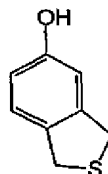
Table 29

Preparation	Precursor		data
95	Prep 90		δ_H (CDCl ₃ , 400 MHz) 2.98 (3H, s), 3.10 (2H, m), 4.39 (2H, m), 6.67 (1H, dd), 6.76 (1H, s), 6.81 (1H, d), 7.33 (1H, dd), 7.49 (1H, s); MS m/z (TS ⁺) 380 (MNH ₄ ⁺)
96	Prep 92		δ_H (CDCl ₃ , 300 MHz) 2.51 (3H, s), 3.06 (3H, s), 6.52 (1H, br), 6.92 (1H, d), 7.02 (1H, dd), 7.14 (1H, d), 7.24 (1H, d), 7.41 (1H, dd), 7.57 (1H, d); MS m/z (ES ⁺) 391 (MNa ⁺)
97	Prep 91		δ_H (CDCl ₃ , 400 MHz) 2.43 (3H, s), 3.02 (3H, s), 6.41 (1H, brs), 6.72-6.85 (2H, m), 6.92 (1H, d), 7.28 (1H, t), 7.38 (1H, d), 7.51 (1H, s); MS m/z (ES ⁺) 351 (MH ⁺)
98	Prep 93		δ_H (CDCl ₃ , 400 MHz) 2.19 (3H, s), 2.42 (3H, s), 2.99 (3H, s), 6.81 (1H, d), 6.86 (2H, m), 7.15 (1H, d), 7.33 (1H, d), 7.51 (1H, s); MS m/z (TS ⁺) 366 (MNH ₄ ⁺)
99	Prep 94		δ_H (CDCl ₃ , 400 MHz) 2.31 (3H, s), 2.43 (3H, s), 3.02 (3H, s), 6.61 (1H, s), 6.72 (1H, dd), 6.83 (1H, d), 6.88 (1H, s), 7.17 (1H, d), 7.37 (1H, dd), 7.55 (1H, s); MS m/z (TS ⁺) 366 (MNH ₄ ⁺)

PREPARATION 100*N*-[3-Cyano-4-[3-methyl-4-(methylsulfanyl)phenoxy]phenyl]-*N*-5 methylmethanesulfonamide

The title compound was prepared from the sulfonamide of Preparation 98 by the method of Preparation 88; δ_H (CDCl₃, 400 MHz) 2.31 (3H, s), 2.44 (3H, s), 2.83 (3H, s), 3.27 (3H, s), 6.79 (1H, d), 6.88 (2H, m), 7.17 (1H, d), 7.44 (1H, dd), 7.58 (1H, d); MS m/z (ES⁺)

10 385 (MNa⁺).

PREPARATION 1011,3-Dihydro-2-benzothiophen-5-ol(i) Preparation of [4-(allyloxy)-2-(hydroxymethyl)phenyl]methanol

- 5 Dimethyl 4-(allyloxy)phthalate [prepared according to Inouye, M.; Tsuchiya, K.; Kitao, T. *Angew. Chem.* 1992, 104, 198-200 (See also *Angew. Chem., Int. Ed. Engl.*, 1992, 204-205)] (9.9 g, 38 mmol) was dissolved in THF (40 mL) and cooled to 0°C before the dropwise addition of lithium aluminium hydride (1M in THF, 77 mL, 77 mmol) over 10 min. The mixture was then allowed to stir at room temperature for 3 h before being
- 10 quenched cautiously by the addition of water (1.4 mL) followed by 2M NaOH (1.4 mL). Excess MgSO₄ was then added followed by water until a granular precipitate formed (ca. 5 mL). The mixture was then filtered and evaporated to a brown oil (7.1 g, ca. 95%). ¹H NMR showed the material to be of ca. 85% purity. It was used directly in the next stage without further purification; δ_H (CDCl₃, 400 MHz) 2.63 (1H, brs), 2.91 (1H, brs), 4.52 (2H, m), 4.67 (4H, m), 5.26 (1H, dd), 5.38 (1H, dd), 5.97-6.09 (1H, m), 6.80 (1H, dd), 6.92
- 15 (1H, d), 7.22 (1H, d).

(ii) Preparation of 5-(allyloxy)-1,3-dihydro-2-benzothiophene

- Crude diol from stage (i) (3.5 g, 18 mmol) was dissolved in DCM (60 mL) and treated with Et₃N (10 mL, 72 mmol) and the solution was cooled to 0°C. Methanesulfonyl
- 20 chloride (4.2 mL, 54 mmol) was added dropwise and the solution was stirred for 1 h being allowed to reach room temperature. The reaction was then quenched by the addition of water followed by 2M HCl (50 mL). The DCM layer was separated and the aqueous layer was re-extracted with DCM (50 mL). The combined organic fractions were washed with water (50 mL), dried (MgSO₄) and concentrated to a volume of ca. 30 mL.
- 25 Benzyltriethylammonium chloride (1 g) was added followed by a solution of sodium sulfide (5 g, 91 mmol) in water (50 mL). The mixture was stirred rapidly under a nitrogen atmosphere for 15 h. The organic layer was separated and the aqueous layer was re-extracted with DCM (50 mL). The combined organic layers were dried (MgSO₄) and evaporated to a yellow oil. Flash chromatography afforded two fractions; the first was
- 30 pure product and the second product contaminated with dimeric material. Trituration of the second fraction caused crystallisation of the dimeric material which was removed by filtration. The filtrate was combined with the first chromatography fraction to afford the

desired product (800 mg, 23%); δ_H (CDCl₃, 400 MHz) 4.16 (2H, s), 4.19 (2H, s), 4.48 (2H, m), 5.26 (1H, d), 5.37 (1H, d), 5.95-6.06 (1H, m), 6.74 (2H, m), 7.09 (1H, d).

(iii) Preparation of 1,3-dihydro-2-benzothiophen-5-ol

The allyl ether from stage (ii) (800 mg, 4.16 mmol) was dissolved in THF (10 mL) and
5 treated with palladium tetrakis(triphenylphosphine) (481 mg, 0.42 mmol) followed by sodium borohydride (944 mg, 25 mmol). The mixture was then heated to 45 °C and stirred at this temperature for 15 h. After cooling to room temperature the THF was evaporated and the residue partitioned between 2M NaOH solution (25 mL) and diethyl ether (25 mL). The aqueous layer was separated and the organic layer re-extracted with
10 2M NaOH solution (25 mL). The combined aqueous layers were neutralised to pH 7-8 with concentrated hydrochloric acid and extracted with EtOAc (2 x 25 mL). The combined organic extracts were dried (MgSO₄) and evaporated to a clear oil of the title phenol which solidified upon standing (540 mg, 85%); 4.14 (2H, s), 4.17 (2H, s), 6.63-6.68 (2H, m), 7.04 (1H, d).

15

Biological Activity

A number of compounds were tested for biological activity by their ability to inhibit the uptake of serotonin by human serotonin transporters as follows.

20 (i) Cell Culture

Human embryonic kidney cells (HEK-293) stably transfected with either the human serotonin transporter (hSERT), noradrenaline transporter (hNET) or dopamine transporter (hDAT) were cultured under standard cell culture techniques (cells were grown at 37°C and 5% CO₂ in DMEM-culture media
25 (supplemented with 10% dialysed foetal calf serum (FCS), 2mM l-glutamine and 250µg/ml geneticin)). Cells were harvested for the assay to yield a cell suspension of 750,000 cells/ml.

(i) Determination of inhibitor potency

30 All test compounds were dissolved in 100% DMSO and diluted down in assay buffer to give appropriate test concentrations. Assays were carried out in 96-well filter bottom plates. Cells (7500 cells/assay well) were pre-incubated in standard assay buffer containing either test compound, standard inhibitor or compound vehicle (1% DMSO) for 5 minutes. Reactions were started by addition of either
35 ³H-Serotonin, ³H-Noradrenaline or ³H-Dopamine substrates. All reactions were

carried out at room temperature in a shaking incubator. Incubation times were 5 minutes for the hSERT and hDAT assays and 15 minutes for the hNET assay. Reactions were terminated by removal of the reaction mixture using a vacuum manifold followed by rapid washing with ice cold assay buffer. The quantity of ^3H -substrate incorporated into the cells was then quantified.

Assay plates were dried in a microwave oven, scintillation fluid added, and radioactivity measured. Potency of test compounds was quantified as IC_{50} values (concentration of test compound required to inhibit the specific uptake of radiolabelled substrate into the cells by 50%).

(iii) Standard Assay Buffer Composition:

Trizma hydrochloride (26mM)

NaCl (124mM)

KCl (4.5mM)

KH_2PO_4 (1.2mM)

$\text{MgCl}_2 \cdot 6\text{H}_2\text{O}$ (1.3mM)

Ascorbic acid (1.136mM)

Glucose (5.55mM)

pH 7.40

CaCl_2 (2.8mM)

Pargyline (100 μM)

Note: The pH of the buffer was adjusted to 7.40 with 1M NaOH before addition of CaCl_2 and pargyline.

(iv) Summary of Assay Parameters

	hSERT Assay	hDAT Assay	hNET Assay
Cell concentration per assay well.	75,000	75,000	75,000
Substrate Concentration.	^3H -5HT (50nM)	^3H -Dopamine (200nM)	^3H -Noradrenaline (200nM)
Incubation time (minutes)	5	5	15

Compounds having a serotonin re-uptake inhibition (SRI) IC_{50} value of less than or equal to 100nM include the title compounds of Examples 1-6, 8-23, 25, 26, 29-32, 34-36, 43, 45-49, 51, 56-102, 109-130.

5

Compounds having an serotonin re-uptake inhibition (SRI) IC_{50} value of less than or equal to 100nM and which are more than 10-fold as potent in the inhibition of serotonin re-uptake than in the inhibition of dopamine re-uptake or noradrenaline re-uptake include the title compounds of Examples 1-6, 9-13, 16-19, 21, 22, 25, 26, 29-32, 34-36, 43, 45,

10

47-49, 51, 57-88, 90-102, 109-121, 123, 124, 127, 129.

Compounds having an serotonin re-uptake inhibition (SRI) IC_{50} value of less than or equal to 100nM and which are more than 100-fold as potent in the inhibition of serotonin re-uptake than in the inhibition of dopamine re-uptake or noradrenaline re-uptake include

15

the title compounds of Examples 1, 2, 4, 5, 9, 12, 13, 16-19, 21, 22, 25, 26, 29-32, 34-36, 43, 45, 48, 49, 58-80, 83-88, 90, 92-97, 99-102, 111-113, 115-118, 120, 123, 124, 127.

Compounds having an serotonin re-uptake inhibition (SRI) IC_{50} value of less than or equal to 50nM and which are more than 100-fold as potent in the inhibition of serotonin re-uptake than in the inhibition of dopamine re-uptake and noradrenaline re-uptake include the title compounds of Examples 1, 2, 4, 9, 12, 17, 18, 26, 29, 30, 36, 43, 45, 48, 49, 60-66, 68-75, 78, 79, 90, 92-94, 100, 102, 116, 118, 124.

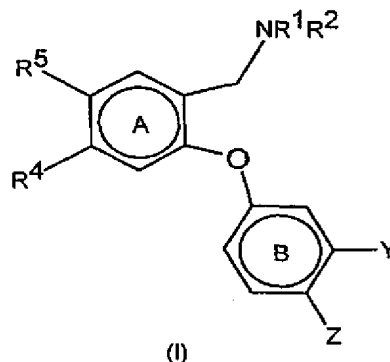
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In particular, the title compound of Example 16 had a serotonin re-uptake inhibition (SRI) IC_{50} of 4.7 nM; the title compound of Example 29 had a serotonin re-uptake inhibition (SRI) IC_{50} of 2.0 nM; and the title compound of Example 62 had a serotonin re-uptake inhibition (SRI) IC_{50} of 3.7 nM.

25

Claims

- 1 A compound of general formula (I), pharmaceutically acceptable salts, solvates or polymorphs thereof;



- 5 wherein;
- R^1 and R^2 , which may be the same or different, are H, C_1 - C_6 alkyl or $(CH_2)_d(C_3$ - C_6 cycloalkyl) wherein $d = 0, 1, 2$ or 3 ; or R^1 and R^2 together with the nitrogen to which they are attached form an azetidine ring;
- 10 Z or Y is $-SR^3$ and the other Z or Y is halogen or $-R^3$; wherein R^3 is independently C_1 - C_4 alkyl optionally substituted with fluorine; except that R^3 is not CF_3 ; or Z and Y are linked so that, together with the interconnecting atoms, Z and Y form a fused 5 to 7-membered carbocyclic or heterocyclic ring which may be saturated, unsaturated or aromatic, and wherein when Z and Y form a heterocyclic ring, in addition to carbon atoms, the linkage contains one or two heteroatoms independently selected from oxygen, sulfur and nitrogen;
- 15 with the proviso that when R^5 is fluorine and R^2 is methyl then the fused ring is not 1,3-dioxalane and Z and Y together do not form a fused phenyl ring;
- R^4 and R^5 , which may be the same or different, are:
- 20 A-X, wherein A = $-CH=CH-$ or $-(CH_2)_p-$ where p is 0, 1 or 2; X is hydrogen, F, Cl, Br, I, $CONR^6R^7$, $SO_2NR^6R^7$, $SO_2NHC(=O)R^6$, OH, C_{1-4} alkoxy, $NR^8SO_2R^9$, NO_2 , NR^6R^{11} , CN, CO_2R^{10} , CHO, SR^{10} , $S(O)R^9$ or SO_2R^{10} ; R^6 , R^7 , R^8 and R^{10} which may be the same or different, are hydrogen or C_{1-6} alkyl optionally substituted independently by one or more R^{12} ; R^9 is C_{1-6} alkyl optionally substituted independently by one or more R^{12} ; R^{11} is hydrogen, C_{1-6} alkyl optionally substituted independently by one or more R^{12} , $C(O)R^6$, CO_2R^9 , $C(O)NHR^6$ or $SO_2NR^6R^7$; R^{12} is F, OH, CO_2H , C_{3-6} cycloalkyl, NH_2 , $CONH_2$, C_{1-6} alkoxy, C_{1-6} alkoxycarbonyl or a 5- or 6-membered heterocyclic
- 25

ring containing 1, 2 or 3 heteroatoms selected from N, S and O optionally substituted independently by one or more R^{13} ; or R^6 and R^7 , together with the nitrogen to which they are attached, form a 4-, 5- or 6-membered heterocyclic ring optionally substituted independently by one or more R^{13} ;

5

or

a 5- or 6-membered heterocyclic ring containing 1, 2 or 3 heteroatoms selected from N, S and O, optionally substituted independently by one or more R^{13} ; wherein R^{13} is hydroxy, C_1 - C_4 alkoxy, F, C_1 - C_6 alkyl, haloalkyl, haloalkoxy, $-NH_2$, $-NH(C_1$ - C_6 alkyl) or $-N(C_1$ - C_6 alkyl) $_2$.

10

2 A compound according to claim 1, pharmaceutically acceptable salts, solvates or polymorphs thereof, wherein R^1 and R^2 , which may be the same or different, are hydrogen or C_1 - C_6 alkyl.

15

3 A compound according to claims 1 or 2, pharmaceutically acceptable salts, solvates or polymorphs thereof, wherein when Z or Y is $-SR^3$, R^3 is methyl or ethyl.

20

4 A compound according to claims 1 or 2, pharmaceutically acceptable salts, solvates or polymorphs thereof, wherein when Z and Y are linked to form a fused ring, the ring is a heterocyclic ring.

25

5 A compound according to claim 4, pharmaceutically acceptable salts, solvates or polymorphs thereof, wherein in addition to carbon atoms, the linkage contains one or two sulfur atoms.

30

6 A compound according to any preceding claim, pharmaceutically acceptable salts, solvates or polymorphs thereof, wherein R^6 and R^7 , which may be the same or different, are hydrogen, C_1 - C_3 alkyl optionally substituted by hydroxy, $-CONH_2$ or C_1 - C_3 alkoxy.

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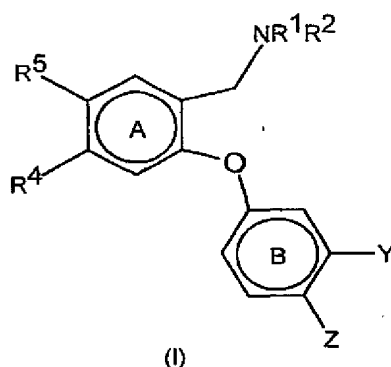
7 A compound according to any preceding claim, pharmaceutically acceptable salts, solvates or polymorphs thereof, wherein R^8 is hydrogen, hydroxyethyl or methyl.

- 8 A compound according to any preceding claim, pharmaceutically acceptable salts, solvates or polymorphs thereof, wherein R⁹ is methyl, ethyl, isopropyl, trifluoromethyl or methoxyethyl.
- 5 9 A compound according to any preceding claim, pharmaceutically acceptable salts, solvates or polymorphs thereof, wherein p is 1 or 0.
- 10 A compound according to any preceding claim, pharmaceutically acceptable salts, solvates or polymorphs thereof, wherein R⁴ and R⁵, which may be the same or different, are
- 10 -(CH₂)_p-X, where p is 0, 1 or 2; X is hydrogen, hydroxy, CONR⁶R⁷, SO₂NR⁶R⁷, NR⁸SO₂R⁹, SR¹⁰, SOR⁹ or SO₂R¹⁰ wherein R⁶, R⁷, R⁸, R⁹ and R¹⁰ are as defined in claim 1, or
- 15 a 5- or 6-membered heterocyclic ring containing 1, 2 or 3 heteroatoms selected from N, S and O.
- 11 A compound according to any preceding claim, pharmaceutically acceptable salts, solvates or polymorphs thereof, wherein R⁴ and R⁵, which may be the same or different, are:
- 20 -(CH₂)_p-X, where p is 0 or 1; X is hydrogen, hydroxy, CONR⁶R⁷, SO₂NR⁶R⁷ or NR⁸SO₂R⁹; wherein R⁶ and R⁷, which may be the same or different, are hydrogen or C₁-C₃alkyl optionally substituted by hydroxy, -CONH₂ or C₁-C₃alkoxy (preferably methoxy); R⁸ is hydrogen, hydroxyethyl or methyl; or R⁹ is methyl, ethyl, isopropyl, trifluoromethyl or methoxyethyl; or
- 25 triazolyl, imidazolyl or pyrazolyl.
- 12 A compound according to any preceding claim, pharmaceutically acceptable salts, solvates or polymorphs thereof, wherein R⁴ and R⁵ are not both hydrogen.
- 30 13 A compound according to any preceding claim, pharmaceutically acceptable salts, solvates or polymorphs thereof, wherein R⁴ is hydrogen.
- 14 A compound according to claim 1, pharmaceutically acceptable salts, solvates or polymorphs thereof, selected from the group:

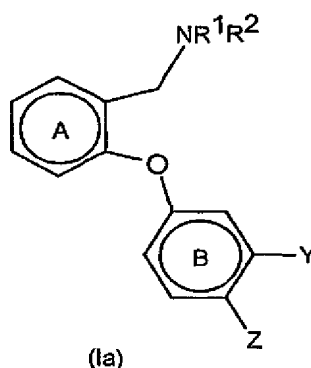
- 4-(2,3-dihydro-1-benzothien-5-yloxy)-3-[(methylamino)methyl]-
benzenesulfonamide (Example 2);
3-[(dimethylamino)methyl]-4-[3-methyl-4-(methylsulfanyl)phenoxy]-
benzenesulfonamide (Example 12);
5 4-(2,3-dihydro-1-benzothien-5-yloxy)-3-[(dimethylamino)methyl]-
benzenesulfonamide (Example 16);
4-[3-chloro-4-(methylsulfanyl)phenoxy]-3-[(dimethylamino)methyl]-
benzenesulfonamide (Example 17);
3-[(dimethylamino)methyl]-4-[3-fluoro-4-(methylsulfanyl)phenoxy]-
10 benzenesulfonamide (Example 18);
N,N-dimethyl-*N*-[2-(6-quinolinyloxy)benzyl]amine (Example 29);
3-[(methylamino)methyl]-4-(6-quinolinyloxy)benzenesulfonamide (Example 35);
4-(2,3-dihydro-1-benzothien-5-yloxy)-3-[(methylamino)methyl]benzamide
(Example 60);
15 4-(2,3-dihydro-1-benzothien-5-yloxy)-*N*-methyl-3-[(methylamino)methyl]-
benzamide (Example 62);
N-{3-[(methylamino)methyl]-4-[3-methyl-4-
(methylsulfanyl)phenoxy]benzyl}methanesulfonamide (Example 75);
3-[(methylamino)methyl]-4-[3-methyl-4-(methylsulfanyl)phenoxy]benzamide
20 (Example 79);
4-(2,3-dihydro-1,4-benzoxathiin-7-yloxy)-3-[(dimethylamino)methyl]benzamide
(Example 88);
{3-[(dimethylamino)methyl]-4-[3-fluoro-4-(methylsulfanyl)phenoxy]phenyl}-
methanol (Example 90);
25 3-[(dimethylamino)methyl]-4-(6-quinolinyloxy)benzamide (Example 100);
3-[(methylamino)methyl]-4-(6-quinolinyloxy)benzamide (Example 102);
N-methyl-*N*-{3-[(methylamino)methyl]-4-[3-methyl-4-(methylsulfanyl)phenoxy]-
phenyl}methanesulfonamide (Example 116) and
N-{4-(2,3-dihydro-1,4-benzoxathiin-7-yloxy)-3-[(dimethylamino)methyl]phenyl}-
30 methanesulfonamide (Example 124).
- 15 A compound as defined in any preceding claim, pharmaceutically acceptable
salts, solvates or polymorphs thereof, for use as a pharmaceutical.

- 16 A pharmaceutical formulation containing a compound as defined in any one of claims 1 to 14, or pharmaceutically acceptable salts, solvates or polymorphs thereof, and a pharmaceutically acceptable adjuvant, diluent or carrier.
- 5 17 The use of a compound as defined in any of claims 1 to 14, pharmaceutically acceptable salts, solvates or polymorphs thereof, in the manufacture of a medicament for the treatment or prevention of a disorder in which the regulation of monoamine transporter function is implicated.
- 10 18 The use according to claim 17 wherein the disorder is depression, attention deficit hyperactivity disorder, obsessive-compulsive disorder, post-traumatic stress disorder, substance abuse disorders or sexual dysfunction.
- 15 19 The use according to claim 18 wherein the disorder is premature ejaculation.
- 20 20 A method of treatment or prevention of a disorder in which the regulation of monoamine transporter function is implicated, comprising the administration of an effective amount of a compound as defined in any one of claims 1 to 14, pharmaceutically acceptable salts, solvates or polymorphs thereof, to a patient in need of such treatment or prevention.
- 20 21 A method of treatment or prevention of premature ejaculation, comprising the administration of an effective amount of a compound as defined in any one of claims 1 to 14, pharmaceutically acceptable salts, solvates or polymorphs thereof, to a patient in need of such treatment or prevention.
- 25 22 A method of increasing ejaculatory latency which comprises the administration of an effective amount of a compound as defined in any one of claims 1 to 14, pharmaceutically acceptable salts, solvates or polymorphs thereof, to a male desiring increased ejaculatory latency.
- 30 23 A process for the preparation of a compound of general formula (I);

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wherein R^1 , R^2 , R^4 , R^5 , X and Z are as defined in any one of claims 1 to 14 comprising reacting a compound of general formula Ia



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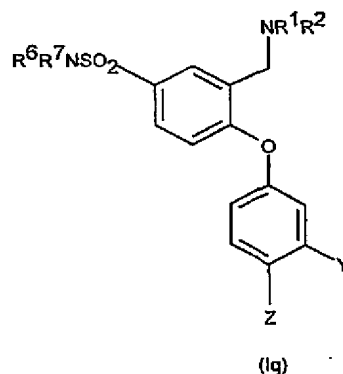
under suitable reaction conditions to form the compound of formula I, wherein the suitable reaction conditions are:

- i) where R^4/R^5 are halogen, by reaction of (Ia) with a suitable halogenating agent in an inert solvent which does not adversely affect the reaction;
- 10 ii) where R^4/R^5 are $-NO_2$, by reaction of (Ia) with a suitable nitrating agent in an inert solvent which does not adversely affect the reaction at, or below, room temperature; or
- ii) where R^4/R^5 is $-SO_2NR^6R^7$ by reaction of an intermediate sulfonyl chloride with the requisite amine of formula HNR^6R^7 in a suitable solvent.

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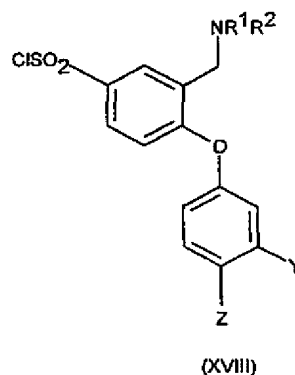
- 24 A process according to claim 23 for preparing a compound of formula (Iq), i.e. a compound of formula I where R^5 is $-SO_2NR^6R^7$ and R^4 is hydrogen,

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comprising

- a) reacting a compound of formula 1a, optionally in a suitable solvent, with chlorosulfonic acid to give a compound of formula XVIII



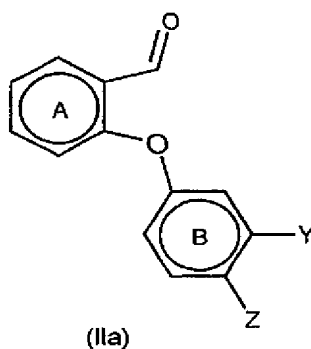
followed by

- b) reacting with HNR^6R^7 to give the compound of formula (Iq).

- 25 A process according to claim 24 wherein the compound of formula XVIII is
 10 generated *in situ* and reacted with HNR^6R^7 without isolation.
- 26 A process according to any one of claims 23 to 25 which further comprises the
 step of preparing compounds of formula (Ia), by reacting compounds of formula
 (IIa)

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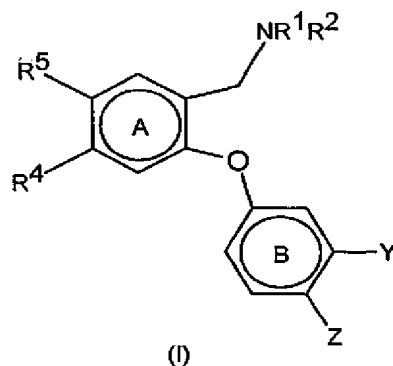
with a compound of formula HNR^1R^2 , or with a suitable salt form thereof, together with a hydride reducing agent in a suitable solvent, to form the compound of formula (Ia).

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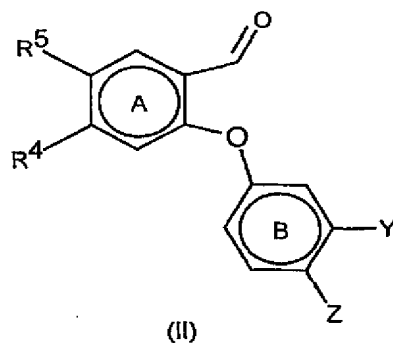
27 An intermediate compound of formula (IIa) or (XVIII) as defined in claims 23 to 26.

28 A process for preparing a compound of formula I

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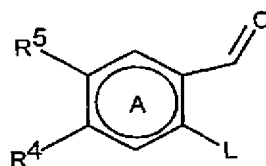
wherein R^1 , R^2 , R^4 , R^5 , X and Z are as defined in any one of claims 1 to 14, comprising reacting compounds of formula II



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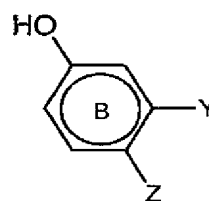
with a compound of formula HNR^1R^2 or with a suitable salt form thereof, together with a hydride reducing agent in a suitable solvent.

- 29 A process according to claim 28 which further comprises coupling under suitable
5 reaction conditions a compound of formula III,



(III)

wherein L is a suitable leaving group such as halogen or a sulfonate ester such as trifluoromethanesulfonate or methanesulfonate, with a compound of formula IV



(IV)

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to give the compound of formula II.

- 30 An intermediate compound of formula II as defined in claim 28.

15

- 31 A compound of general formula (I), or pharmaceutically acceptable salts, solvates or polymorphs thereof, wherein R^1 , R^2 , Y and Z are as defined in claim 1; and R^4 and R^5 , which may be the same or different, are $-(\text{CH}_2)_p\text{-A}'$, wherein p is 0, 1 or 2 and A' is a polar group.

20

- 32 A compound according to claim 23, wherein the polar group has a δ -value more negative than -0.1.

INTERNATIONAL SEARCH REPORT

Int'l Application No

PCT/IB 01/01521

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C07C323/20 C07D333/54 C07D327/06 C07D307/87 C07D333/72
 C07C311/37 C07D215/18 C07D239/74 C07D277/62 A61K31/18
 A61K31/38 A61K31/39 A61K31/34 A61K31/135 A61K31/47

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07C C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

BEILSTEIN Data, CHEM ABS Data, EPO-Internal, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 5 691 373 A (EDMUNDS JEREMY JOHN ET AL) 25 November 1997 (1997-11-25) example 323 ---	27, 30
X	WO 99 47497 A (MERCK FROSST CANADA INC ; BELLEY MICHEL (CA); GAREAU YVES (CA); JUT) 23 September 1999 (1999-09-23) page 81, line 31 - line 35 ---	27, 30
P, X	WO 00 50380 A (HOWARD HARRY RALPH JR ; SEEGER THOMAS FRANCIS (US); PFIZER PROD INC) 31 August 2000 (2000-08-31) page 26, preparation 6 ---	30
A	EP 0 516 234 A (AKZO NV) 2 December 1992 (1992-12-02) page 2, line 7 - line 17; claims; examples --- -/--	1-32



Further documents are listed in the continuation of box C.



Patent family members are listed in annex.

* Special categories of cited documents:

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the international filing date
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- *G* document member of the same patent family

Date of the actual completion of the international search

22 November 2001

Date of mailing of the international search report

05/12/2001

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INTERNATIONAL SEARCH REPORT

In al Application No

PCT/IB 01/01521

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 A61K31/495 A61K31/425

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 97 17325 A (FARMAK A S ; POLIVKA ZDENEK (CZ); DOBROVSK KAREL (CZ); SILHANKOVA A) 15 May 1997 (1997-05-15) page 1, paragraph 1; claims; examples	1-32
L	WO 01 72687 A (MIDDLETON DONALD STUART ; STOBIE ALAN (GB); HEPWORTH DAVID (GB); PF) 4 October 2001 (2001-10-04)	

☐ Further documents are listed in the continuation of box C.☒ Patent family members are listed in annex.

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- *P* document published prior to the international filing date but later than the priority date claimed

- *T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- *X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- *Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
- *&* document member of the same patent family

Date of the actual completion of the international search

22 November 2001

Date of mailing of the international search report

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Seufert, G

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

The compounds mentioned on page 7 of the application are not included in the scope of the claims and have not been searched. Furthermore, it is not clear what compounds are encompassed by the vague and undefined terms "prodrugs", "promoieties" or "protected derivatives", which, according to the description (see page 11) are meant to be part of the invention. Therefore, the search has been carried out only for those compounds, which are defined by the claims.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT

In International Application No
PCT/IB 01/01521

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